In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: June 17, 2019

LISA FAUP, on behalf of A.F., a minor,	*	No. 12-87V
Petitioner,	*	Special Master Sanders
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Diphtheria-Tetanus-acellular-Pertussis ("DTaP") Vaccine; Inactivated Polio ("IP") Vaccine; Systemic Juvenile Idiopathic Arthritis ("sJIA"); *Althen* Causation
Respondent.	*	

Sylvia Chin-Caplan, Law Office of Sylvia Chin-Caplan, Boston, MA, for Petitioner.
Jennifer L. Reynaud, United States Department of Justice, Washington, D.C., for Respondent.

DECISION ON ENTITLEMENT[1]

On February 9, 2012, Lisa Faup ("Petitioner") filed a petition on behalf of A.F., a minor, pursuant to the National Vaccine Injury Compensation Program,[2] 42 U.S.C. §§ 300aa-10 to 34 (2012). Petitioner alleged that A.F. suffered from a "rheumatologic injury" as a result of the Diphtheria-Tetanus-acellular-Pertussis ("DTaP") and inactivated polio ("IP") vaccines she received on March 13, 2009. Pet. at 1, ECF No. 1. On October 5, 2012, Petitioner amended the petition to allege that A.F.'s vaccines caused her to develop systemic[3] juvenile idiopathic arthritis[4] ("sJIA"). Am. Pet. at 1, ECF No. 19.

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[1] This decision shall be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet**. In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755 ("the Vaccine Act" or "Act"). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

[3] "Pertaining to or affecting the body as a whole." *Dorland's Illustrated Medical Dictionary* 1865 (32nd ed. 2012) [hereinafter "*Dorland's*"].

[4] Juvenile idiopathic arthritis is a type of "rheumatoid arthritis [seen] in children, with swelling, tenderness, and pain in one or more joints, which may lead to impaired growth and development, limitation of movement, ankylosis, and flexion contractures." *Dorland's* at 150.

The undersigned held an entitlement hearing in this matter on March 13–14, 2018, in Washington, D.C. After considering the record as a whole, and for the reasons explained below, the undersigned finds that Petitioner has failed to show that A.F.'s condition was caused by the alleged vaccines and is therefore not entitled to compensation under the Vaccine Act.

I. Procedural History

The undersigned detailed the procedural history of this case in the decision granting interim attorneys' fees and costs, issued on April 21, 2017. ECF No. 83.

Petitioner submitted medical records over the four months following the filing of her petition. ECF Nos. 8, 10. Respondent filed his Rule 4(c) report on June 18, 2012. ECF No. 12. Respondent argued that Petitioner's claim should be dismissed because she could not show that A.F. suffered from her condition for more than six months. Resp't's Report at 12–13, ECF No. 12. Respondent also alleged that Petitioner had not provided a medical theory causally linking A.F.'s injuries with the vaccines she received on March 13, 2009. *Id.* During a subsequent status conference, the special master assigned to the case at the time ordered Respondent to submit a motion for summary judgment based upon the six-month severity requirement. ECF No. 14. Respondent submitted this motion on August 17, 2012. ECF No. 15.

In his motion, Respondent argued that evidence that A.F. was treated by medication beyond six months was not sufficient to satisfy the Vaccine Act's six-month requirement. *Id.* at 8–10. On February 26, 2013, the presiding special master found that she could not rule on the motion without "testimony from either a treating physician or an expert" on "whether A.F.'s abnormal laboratory test results were indicative of ongoing problems with JIA; and . . . [on] whether A.F.'s normal bone marrow biopsy constituted a surgical intervention under the Vaccine Act." Ruling Denying Mot. for Summary Judgment, ECF No. 23 at 8. Petitioner submitted an expert report in response to the special master's ruling on September 12, 2013, ECF No. 30, and Respondent filed a responsive expert report on January 13, 2014. ECF No. 32.

On May 20, 2014, Respondent filed his second motion for summary judgment. ECF No. 34. This motion was denied in a ruling issued on January 15, 2015. Order Denying Mot. for Summary Judgment, ECF No. 37. The presiding special master found that "the ongoing need for medication to prevent symptoms and/or relapse of the alleged vaccine-caused illness constitutes a residual effect or complication of that illness." *Id.* at 6. Following this decision, the parties submitted expert reports through June and August of 2015 regarding Petitioner's theory of causation. ECF Nos. 44 and 45. Petitioner submitted a second supplemental expert report on February 5, 2016. ECF No. 51. Respondent submitted a responsive expert report on August 4, 2016. ECF No. 60.

On January 10, 2017, the undersigned was assigned to the case. Not. of Reassignment, ECF No. 71. On February 8, 2017, Ms. Sylvia Chin-Caplan was substituted in as Petitioner's counsel. ECF No. 75. Petitioner immediately filed a motion for interim attorneys' fees and costs for the work performed by her former counsel, Mr. Ronald Homer. ECF No. 74. Petitioner then submitted another expert report on February 13, 2017. ECF No. 76. On April 21, 2017, the undersigned issued a decision awarding interim attorneys' fees and costs to Petitioner's former

counsel. ECF No. 83. On May 30, 2017, Respondent submitted another responsive expert report. ECF No. 86.

An entitlement hearing was held in Washington, D.C., on March 13–14, 2018. ECF No. 91. Following the hearing, the parties submitted post-hearing briefs. *See* Minute Entry, dated Mar. 14, 2018. Petitioner submitted her post-hearing brief on May 30, 2018, ECF No. 116, and Respondent submitted his on August 3, 2018. ECF No. 118. Petitioner submitted a post-hearing reply brief on September 4, 2018. ECF No. 119.

This matter is now ripe for adjudication.

II. Factual Background

A. Medical Records

A.F. was born on March 9, 2004, the oldest of a set of female triplets. Pet'r's Ex. 1 at 1, 14, ECF No. 8-1. A.F. and her sisters were born prematurely at thirty-five weeks with no health concerns. *Id.* at 22–23. At the age of seven weeks, A.F. underwent a cardiac evaluation for a detected heart murmur. *Id.* at 27. She was diagnosed with an "innocent heart murmur" but was "otherwise normal." *Id.* at 28; *see also* Pet'r's Ex. 28 at 10, ECF No. 65-5. On March 2, 2009, A.F. was seen by her pediatrician for an otitis media[5] and given a seven-day course of amoxicillin.[6] Pet'r's Ex. 15 at 1, ECF No. 10-1; Pet'r's Ex. 1 at 72. A.F.'s early medical history was otherwise unremarkable, and she had all her early immunizations without incident. Pet'r's Ex. 1 at 2.

On March 13, 2009, A.F. received the DTaP and IP vaccinations at issue in this case. Pet'r's Ex. 1 at 2, 8; Pet'r's Ex. 15 at 1. On March 20, 2009, Petitioner took A.F. to Island Heights Pediatrics because she had been suffering from a maculopapular rash[7] over the previous three days. Pet'r's Ex. 1 at 16; Pet'r's Ex. 15 at 1. A.F. was afebrile and tested negative for strep throat. Pet'r's Ex. 1 at 16; Pet'r's Ex. 11 at 2, ECF No. 8-11. She was given prednisone[8] for the rash. Pet'r's Ex. 15 at 1. On March 25, 2009, A.F. presented again to Island Heights Pediatrics for abdominal pain, a swollen knee, and a recurring fever of up to 103 °F.[9] *Id.* The medical records reflect that A.F.'s primary care physician considered a diagnosis of Henoch-Schönlein purpura[10] ("HSP"). *Id.* Two days later, A.F. was seen by an allergist at the Allergy

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[5] Otitis media is defined as "inflammation of the middle ear." *Dorland's* at 1351.

[6] Amoxicillin is defined as "a semisynthetic derivative of ampicillin effective against a broad spectrum of gram-positive and gram-negative bacteria." *Dorland's* at 65.

[7] A maculopapular rash consists of "both flat and raised skin lesions . . . [which] are usually red and can merge together." *What Is a Maculopapular Rash?* HEALTHLINE, https://www.healthline.com/health/skin/maculopapular-rash (last visited May 30, 2019).

[8] Prednisone is defined as "a synthetic glucocorticoid derived from cortisone, administered orally as an antiinflammatory and immunosuppressant in a wide variety of disorders." *Dorland's* at 1509.

[9] The record does not indicate whether A.F. was given any treatment by her parents during those three days.

[10] Henoch-Schönlein purpura is "a form of nonthrombocytopenic purpura, sometimes a type of hypersensitivity vasculitis and sometimes of unknown cause, usually seen in children and associated with

and Asthma Center who could not determine whether A.F.'s rash was allergic or viral in nature. Pet'r's Ex. 3 at 2–4, ECF No. 8-3. The allergist advised Petitioner to take A.F. to the emergency department. *Id.* at 3.

A.F. was admitted to the Robert Wood Johnson University Hospital later that day. Pet'r's Ex. 2 at 2, ECF No. 8-2. The emergency physicians admitted A.F. in order to rule out HSP. *Id.* Petitioner recounted that A.F. had been suffering from her rash for ten days and "ha[d] been having itchiness since then." *Id.* The physicians noted that A.F. had "maculopapular rash to her face, trunk, and extremities" that was "slightly raised" and experienced "mild difficult walking due to discomfort [from itchiness]." *Id.* A.F. was discharged the same day with a diagnosis of HSP. *Id.* at 1. A.F. was given a prescription for Benadryl[11] and instructions to follow up with her primary care physician. *Id.* at 1, 4, 13. On March 31, 2009, A.F. was taken to Richmond Pediatrics for a rash, fever, joint pain, and loss of appetite. Pet'r's Ex. 4 at 1, ECF No. 8-4. The treating physician's impression was that A.F. suffered from HSP. *Id.*

On April 8, 2009, A.F. presented again to Richmond Pediatrics for joint pain, swollen wrists and hands, and a fever of 102–104 °F lasting several days. *Id.* at 2. The treating physician's impression was that A.F. suffered from HSP. *Id.* A.F. was referred to Dr. Yukiko Kimura, a pediatric rheumatologist, by A.F.'s pediatrician, Dr. Ann Marie Grigoletto. *See* Pet'r's Ex. 5 at 1, 5, ECF No. 8-5. A.F. was seen by Dr. Kimura for an initial evaluation on April 16, 2009. *Id.* at 5. Dr. Kimura reviewed A.F.'s medical history and noted that she was having daily ankle, knee, and wrist pain. *Id.* at 1, 7. Dr. Kimura's assessment was that A.F. likely suffered from sJIA of unknown etiology. *Id.* at 9. Dr. Kimura advised Petitioner to give A.F. Motrin[12] or Naprosyn[13] if her fever or joint pain continued. *Id.* A.F. saw Dr. Kimura again on April 28, 2009, for persistent fever lasting several days and continued joint and abdominal pain. *Id.* at 14. Dr. Kimura noted the symptoms but concluded that there had been "some improvement" in A.F.'s sJIA without treatment and prescribed Naprosyn. *Id.* at 15.

A.F. continued to have symptoms of fever and rash through May of 2009. *See id.* at 18–35. On May 13, 2009, a CT scan showed that A.F. suffered from hepatosplenomegaly.[14] Pet'r's Ex. 7 at 1–2, ECF No. 8-7. Between May 21 and May 23, 2009, A.F. had a severe flare-up of her rash and experienced high fever. Pet'r's Ex. 5 at 34; Pet'r's Ex. 1 at 20. On May 26, 2009, A.F. underwent blood tests, which, according to Dr. Kimura, showed a possible episode of macrophage activation syndrome[15] ("MAS"). Pet'r's Ex. 11 at 11; Pet'r's Ex. 1 at 73. Because

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symptoms including urticaria, erythema, arthropathy, arthritis, gastrointestinal symptoms, and renal involvement." *Dorland's* at 1557.

[11] Benadryl is the "trademark for preparations of diphenhydramine hydrochloride," which is "an angiotensin-converting enzyme inhibitor." *Dorland's* at 208.

[12] Motrin is the "trademark for preparations of ibuprofen." *Dorland's* at 1182.

[13] Naprosyn is the "trademark for preparations of naproxen," which in turn is "a nonsteroidal antiinflammatory drug . . . used in the treatment of pain, inflammation, arthritis, rheumatoid arthritis [and] fever." *Dorland's* at 1232.

[14] Hepatosplenomegaly is defined as the "enlargement of the liver and spleen." *Dorland's* at 847.

[15] Macrophage activation syndrome is "a life-threatening complication of rheumatic disease that, for unknown reasons, occurs much more frequently in individuals with systemic juvenile idiopathic arthritis . . . and in those with adult-onset Still disease. Macrophage activation syndrome is characterized by pancytopenia, liver insufficiency, coagulopathy, and neurologic symptoms and is thought to be caused by

MAS is "a hemophagocytic syndrome that can be life threatening in systemic JIA[,]" A.F.'s pediatrician, Dr. Grigoletto, called Petitioner to advise her to take A.F. to hospital "to get the labs repeated immediately." Pet'r's Ex. 1 at 73; Pet'r's Ex. 5 at 30 (record of phone call).

Although A.F. was asymptomatic at that time, Petitioner took A.F. to the Children's Hospital of Philadelphia ("CHOP") emergency department on May 28, 2009. Pet'r's Ex. 1 at 73; Pet'r's Ex. 5 at 30; Pet'r's Ex. 12 at 11, ECF No. 8-12. A.F. was admitted to the emergency department "to get lab values." Pet'r's Ex. 12 at 14. The medical records note that A.F. had been "misdiagnos[ed]" with HSP and that she spent the night in CHOP under observation. *Id.* at 11, 33. Rheumatology assessed A.F.'s condition and confirmed her diagnosis of sJIA. *Id.* at 26. The rheumatology notes state that A.F.'s rash began on March 17, 2009, together with abdominal pain and fever. *Id.* at 23. A.F.'s lab tests "showed some improvement," and she had no issues during her admission. Pet'r's Ex. 1 at 73. A.F. was prescribed Mobic[16] and Petitioner was advised to continue giving her Naprosyn. Pet'r's Ex. 12 at 18, 23. A.F. was discharged on May 29, 2009, without complications. *Id.* at 33. Dr. Kimura wrote that since her discharge, A.F. had "continued to do well and seem[ed] [to have been] back to her pre-illness state." Pet'r's Ex. 1 at 73. Dr. Kimura also suspected that "the fever and rash episode that [A.F.] had [had] early in the week may have been MAS which . . . spontaneously improved since she [was] asymptomatic . . ." *Id.*

Despite the improvement of her symptoms, on June 4, 2009, A.F. underwent a bone marrow evaluation to rule out leukemia or MAS before starting treatment with steroids. Pet'r's Ex. 1 at 65–66. The bone marrow "looked normal and showed no evidence of either malignancy or MAS." *Id.* That same day, Petitioner took A.F. to see Dr. Kimura for "occas[ional] joint pain" and low-grade fever. *Id.* at 66. Dr. Kimura noted that A.F. had swelling in her left and right ankles, an active rash, and low-grade fever. *Id.* at 66–67. She also wrote that A.F.'s sJIA was still active and discussed steroid treatment with Petitioner. *Id.* at 67. Ultimately, Dr. Kimura did not administer steroids at that time, instead increasing A.F.'s Mobic prescription. *Id.* On June 16, 2009, Dr. Kimura saw A.F. for "some rash [and] occas[ional] joint pain," absent fever. *Id.* at 46. Dr. Kimura noted that A.F.'s sJIA was "somewhat better[,] but [her] arthritis persist[ed]." *Id.* at 47. After discussing treatment options with Petitioner, Dr. Kimura decided to begin A.F. on fifteen milligrams of methotrexate.[17] *Id.*

On June 17, 2009, Petitioner took A.F. to see Dr. Thomas Lehman, a pediatric rheumatologist, for an evaluation. Pet'r's Ex. 6 at 1–2, ECF No. 8-6. Dr. Lehman reviewed A.F.'s medical history and noted that "[s]he ha[d] had no recent fever or rash[,] her rash [was] minimal, and [she] only [had] minor joint complaints." *Id.* at 1. Dr. Lehman found that A.F.

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the activation and uncontrolled proliferation of T lymphocytes and well-differentiated macrophages, leading to widespread hemophagocytosis and cytokine overproduction." *Macrophage Activation Syndrome*, MEDSCAPE, http://emedicine.medscape.com/article/1380671-overview (last visited May 30, 2019).

[16] Mobic is the "trademark for a preparation of meloxicam," which in turn is "a nonsteroidal antiinflammatory drug used in the treatment of osteoarthritis[.]" *Dorland's* at 1126, 1171.

[17] Methotrexate is defined as "a folic acid antagonist that acts by inhibiting synthesis of DNA, RNA, thymidylate, and protein . . . It is also used as an antipsoriatic and antiarthritic in the treatment of severe, recalcitrant, disabling psoriasis and severe rheumatoid and psoriatic arthritis." *Dorland's* at 1151.

"ha[d] [a] clearly documented systemic-onset [juvenile rheumatoid arthritis[18]] by history and by laboratory findings." *Id.* at 2. After discussing treatment options with A.F.'s family, Dr. Lehman recommended they begin a low dose of prednisone and advised Petitioner to follow up with A.F.'s primary care physician. *Id.* On June 18, 2009, Petitioner called Dr. Kimura to discuss treating A.F. with prednisone. Pet'r's Ex. 5 at 48. Dr. Kimura explained that "prednisone would do nothing to protect [A.F.'s] joints" and that she did not want to put A.F. on the drug. *Id.* Petitioner agreed and stated she would "fill the prescription for . . . [m]ethotrexate" for A.F. to take over the next few days. *Id.*

A.F. was seen again by Dr. Kimura on July 14, 2009. Pet'r's Ex. 1 at 43. Dr. Kimura noted that A.F. was doing well, with no fever, only an occasional rash, and "no joint pain to speak of." *Id.* Dr. Kimura advised Petitioner to stop the Naprosyn and noted that A.F.'s sJIA was "much better" on methotrexate. *Id.* at 44. A.F. had greatly improved by her next visit to Dr. Kimura on August 27, 2009. *Id.* at 49. Dr. Kimura wrote that A.F. "ha[d] been great[,] [with] no fever, rash, [or] joint pain." *Id.* She noted that A.F. had only trace swelling in her ankles and a low blood count. *Id.* at 50. Petitioner mentioned that A.F. had experienced nausea on methotrexate once but was otherwise "doing well." *Id.* at 49–50. Dr. Kimura did not decrease A.F.'s dosage of methotrexate at that time. *Id.* at 51. A.F. continued to improve, and on December 1, 2009, Dr. Kimura reduced A.F.'s methotrexate dose to 0.5 milligrams weekly. *Id.* at 52–53.

A.F.'s sJIA symptoms continued to improve. On February 2, 2010, Dr. Kimura noted that A.F. had no fever, pain, or rash. *Id.* at 55. Dr. Kimura again reduced A.F.'s methotrexate dosage on April 6, 2010, to 0.15 milligrams weekly. Pet'r's Ex. 5 at 64. On July 13, 2010, Dr. Kimura wrote that A.F. was experiencing "no problems at all." Pet'r's Ex. 1 at 58. Dr. Kimura also wrote that A.F. had stopped taking methotrexate completely six weeks earlier, without a relapse in her symptoms.[19] *Id.* at 58–59. A.F.'s lab results, however, continued to be abnormal. Pet'r's Ex. 5 at 78–79. Specifically, her white blood cell count and creatine levels were low, and her lactate dehydrogenase[20] levels were high. *Id.* Other than an indication that these results were abnormal, no other discussion of the significance of these results is found in the medical records. A.F.'s sJIA symptoms ultimately did not return, and her health has improved. Pet'r's Ex. 18 at 4, ECF No. 18-1.

B. Petitioner's Affidavit

Petitioner submitted one affidavit in this case. *See* Pet'r's Ex. 18. Petitioner wrote that prior to receiving the vaccines in question, A.F. had been "a very active child [who had] enjoyed playing with her sisters, whether it was arts and crafts or running around at the playground." *Id.*

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[18] Another term for JIA. *Dorland's* at 150.

[19] It is unclear on what precise date A.F. stopped taking methotrexate. The medical records do not specify when this happened besides the July 13, 2010 notation from Dr. Kimura.

[20] Lactate dehydrogenase "is an enzyme found in almost every cell of [the] body." The lactate dehydrogenase test "looks for signs of damage to the body's tissues." *What Is a Lactate Dehydrogenase (LDH) Test?* WEBMD, https://www.webmd.com/a-to-z-guides/lactic-acid-dehydrogenase-test#1 (last visited May 30, 2019).

at 1. She also wrote that "[b]y her fifth birthday, [A.F.] was riding her bike without training wheels." *Id.*

Petitioner wrote that A.F. received the DTaP and IP vaccines in question during a physical exam on March 12, 2009, in order to "enroll in kindergarten in the fall[.]" *Id.* She also wrote that A.F.'s health began to deteriorate "[w]ithin the next several days," after developing a rash and experiencing elbow and wrist pain. *Id.* Petitioner described how A.F.'s condition did not improve despite multiple doctor's visits and treatments. *Id.* at 2. Petitioner's account of A.F.'s symptoms and treatment was consistent with the medical record.

Petitioner described a time A.F.'s "body was covered in a rash, her joints remained swollen, and [her] fever persisted. [A.F.] did not want to be touched because physical contact was painful to her frail body." *Id.* Petitioner also wrote that the "family helped [A.F. to] eat and go to the bathroom because she had little strength to do so on her own." *Id.*

Petitioner wrote that A.F.'s weekly methotrexate injections were "a traumatic experience for [the] family[,]" because A.F. "hated receiving the injections, and [Petitioner's] husband and [she] had to hold her down to give her the medicine." *Id.* Petitioner also wrote that A.F.'s "sisters were always by her side showing their support, teary-eyed since they saw how painful the injections were." *Id.* She also described the side effects of methotrexate as "horrible," which left A.F. feeling "nauseous and fatigued following her injections, and [with] a compromised immune system . . . ." *Id.* at 3–4.

Petitioner wrote that A.F.'s health has improved[,]" and she "can once again enjoy activities with her sisters and friends, like riding bikes and playing in the schoolyard." *Id.* at 4. Petitioner also wrote that despite the progress made, the family "still worr[ies] that [A.F.'s] symptoms will return." *Id.*

III. Expert Review[21]

A. Petitioner's Expert, Dr. Robert Sundel, M.D.

Dr. Sundel is a pediatric rheumatologist and is board certified in pediatrics and pediatric rheumatology. Pet'r's Ex. 21 at 1, ECF No. 30-2; Tr. 14:18–19. Dr. Sundel received his medical degree from Boston University in 1982. Pet'r's Ex. 21 at 1. His post-doctoral training includes two years spent as a pediatric resident at the Babies Hospital at Columbia–Presbyterian Medical Center in New York and one year spent as a research associate in cellular immunology at Hadassah Medical Center in Jerusalem, Israel. *Id.* He also spent three years as an allergy/ immunology/rheumatology fellow at the Children's Hospital in Boston, MA. *Id.* As a pediatric rheumatologist, he has seen between one hundred and one hundred and fifty pediatric patients with juvenile arthritis. Tr. 15:3–7.

[21] The undersigned will not discuss Petitioner's exhibit 20 because it specifically addressed the six-month duration issue previously decided by the then assigned special master's ruling issued on January 15, 2015. *See* ECF No. 37.

Dr. Sundel's clinical experience includes thirty years as an attending physician and then as director at the Children's Hospital in Boston, MA. Pet'r's Ex. 21 at 2. He is the current Fred S. Rosen Chair in Pediatric Rheumatology and Director Emeritus of Rheumatology at the Boston Children's Hospital, where he has been employed since 1989. Pet'r's Ex. 21 at 1–2; Tr. 14:3–5. In addition to his clinical experience, Dr. Sundel is an associate professor of pediatrics at Harvard Medical School. Pet'r's Ex. 21 at 1; Tr. 14:14–15. He has authored more than sixty publications, including articles on the treatment of polyarticular juvenile rheumatoid arthritis and of severe systemic onset juvenile rheumatoid arthritis. Pet'r's Ex. 21 at 5–10; Tr. 14:18–20. Dr. Sundel was admitted to testify as an expert in the field of pediatric rheumatology. Tr. 16:11–16.

Dr. Sundel submitted one expert report and two supplemental reports in this case. Pet'r's Ex. 20, ECF No. 30-1; Pet'r's Ex. 23, ECF No. 44-1; Pet'r's Ex. 24, ECF No. 51-1.

1. Dr. Sundel's Expert Report

Dr. Sundel submitted his expert report on September 12, 2013.[22] Pet'r's Ex. 20. Dr. Sundel opined that A.F. "developed systemic onset juvenile idiopathic arthritis after being immunized with DTaP and [IP] vaccines." *Id.* at 2, 4. He noted that A.F. exhibited "no symptoms to suggest an infection, trauma, or other recognized antecedents of arthritis in children." *Id.* at 2. He did state, however, that A.F. had been treated "with amoxicillin for an ear infection" eleven days prior to the vaccination in question. *Id.* at 2. Dr. Sundel also noted that although some types of arthritis develop gradually, A.F.'s sJIA was "far more dramatic and abrupt." *Id.* He explained that A.F.'s "presentation is more commonly associated with infections and other acute challenges to the immune system." *Id.* He concluded that "in the absence of alternative explanations for why [A.F.] developed arthritis, vaccine-associated arthritis is the most plausible hypothesis." *Id.* (citing Pet'r's Ex. 20, Tab E,[23] ECF No. 104-5; Pet'r's Ex. 20, Tab F,[24] ECF No. 30-1).

Dr. Sundel also wrote that A.F.'s normal test results during the early stages of her disease were likely due to the treatments she received at the time. *Id.* at 3. The use of "immunosuppressive and immunomodulatory therapies," he explained, "regularly allows children . . . to achieve sustained, disease-free remissions in conditions that were inexorably crippling in the past." *Id.* He therefore argued that "a child [like A.F.] may have a normal examination and laboratory tests when her arthritis is optimally controlled, even relatively soon after the onset of [her] condition." *Id.*

2. Dr. Sundel's First Supplemental Expert Report

Dr. Sundel submitted his first supplemental report on June 15, 2015. Pet'r's Ex. 23. Dr. Sundel wrote that "the pathogenesis of arthritis [including sJIA] is generally not understood." *Id.*

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[22] Dr. Sundel's report primarily addressed the six-month duration issue upon which two special masters ruled previously and which will not be discussed in this Opinion.

[23] D.P.M. Symmons and K. Chakravarty, *Can Immunisation Trigger Rheumatoid Arthritis?* ANN. RHEUM. DIS. 1993;52:843–44.

[24] C.P. Howson and H.V. Fineberg, *Adverse Events Following Pertussis and Rubella Vaccines. Summary of a Report of the Institute of Medicine*. JAMA 1992;267(3):392–96.

at 3 (citing Pet'r's Ex. 23, Tab A,[25] ECF No. 105-5). But, he agreed with Respondent's expert Dr. Rose that "the innate immune system is central to autoinflammatory disorders" like sJIA. *Id.* at 4.

Dr. Sundel also explained that several theories exist on the triggers of sJIA, "though none ha[ve] been incontrovertibly proven." *Id.* Dr. Sundel wrote that one of these theories is molecular mimicry, which involves the "cross[-]reactivity between bacterial antigens and fragments of human proteins[.]" *Id.* He posited that A.F.'s sJIA was likely not the result of molecular mimicry. *Id.* He explained that "the complex interaction of T- and B-cells necessary to induce the antigen-specific response of molecular mimicry typically takes considerably longer than the week between [A.F.'s] immunizations and the apparent onset of her systemic [JIA]." *Id.*

Dr. Sundel wrote that the Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants ("ASIA") theory "has raised the possibility that triggering of arthritis and other forms of autoimmunity may be the result of immune potentiation by additives to immunizations rather than the vaccines themselves." *Id.* at 3–4 (citing Pet'r's Ex. 23, Tab D,[26] ECF No. 44-1). He noted that "arthritis has been associated with a variety of vaccines and a broad spectrum of incubation periods . . . ." *Id.* at 4 (citing Pet'r's Ex. 23, Tab G,[27] ECF No. 44-1). But "[b]ecause of this variety of potential triggers," he continued, "a direct association with even the most commonly implicated vaccines . . . has been elusive." *Id.* (citing Pet'r's Ex. 23, Tab H,[28] ECF No. 44-1). Dr. Sundel, nonetheless, argued that A.F.'s sJIA "is consistent with the much more rapid response that may occur when an adjuvant triggers pathologic inflammation." *Id.*

Dr. Sundel explained that as an autoinflammatory disorder, sJIA "is more consistent with a process involving [Toll-like receptors[29]] and inflammasomes.[30]" *Id.* Adjuvants, he wrote, "exert their immunomodulatory roles on diverse components of the immune response, . . . including binding to [these] Toll-like receptors . . . and activating the inflammasome system to stimulate innate immune responses." *Id.* Because adjuvants have an effect on both the innate and adaptive immune systems, he explained, they "may [also] augment the release of chemokines[31] and cytokines[32] from cells of the adaptive immune system," thus "perpetuati[ng] . . . the immune response that leads to systemic arthritis." *Id.*

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[25] C.K. Correll and B.A. Binstadt, *Advances in the Pathogenesis and Treatment of Systemic Juvenile Idiopathic Arthritis*. PEDIATRIC RESEARCH 2013;75(1-2):176–83.

[26] Y. Shoenfeld and N. Agmon-Levin, *'ASIA' – Autoimmune/Inflammatory Syndrome Induced by Adjuvants*. JOURNAL OF AUTOIMM. 2011;36(1):4–8.

[27] Vaccine Adverse Event Reporting System, available at http://vaers.hhs.gov/index.

[28] R.P. Chen et al., *Epidemiology of Autoimmune Reactions Induced by Vaccination*. JOURNAL OF AUTOIMM. 2001;16:309–18.

[29] Toll-like receptors are "microbial components [that] are detected by innate signaling pattern recognition receptors" and which "are specialized for detect[ing] . . . different classes of pathogens." *See* Notice of Filing Resp't's Ex. I, Tab 6 at 1, filed on CD-ROM, ECF No. 47.

[30] Inflammasomes are the "the control center of the innate immune system." Tr. 35:1–2.

[31] Chemokines are "a family of low molecular weight . . . cytokines that induce chemotaxis or chemokinesis in leukocytes[.]" *Dorland's* at 340.

[32] Cytokine is the "generic term for nonantibody proteins released by one cell population . . . on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response." *Dorland's* at 466.

Dr. Sundel concluded that despite sparse data on the correlation between adjuvants and vaccine-related complications, recent research supports the contention that aluminum adjuvants play a role "particularly in young girls who develop arthritis shortly after an immunization, typically a booster dose." *Id.* at 5. Dr. Sundel referred to a study by Cerpa-Cruz et al.[33] that analyzed one hundred and twenty patients who developed a medical complication within fifty-four days after receiving a vaccine at several health centers in Guadalajara, Mexico, from 2008 to 2012. *Id.* (citing Pet'r's Ex. 23, Tab L, ECF No. 106-1). He noted that the characteristics of forty-three of the patients "match [A.F.] very closely: [sixty percent] of those developing reactions after receiving vaccinations were children, [fifty-eight percent] of whom were female." *Id.* Dr. Sundel also opined that although an aluminum adjuvant-related causation "cannot be proven retrospectively," his conclusion that A.F.'s sJIA is causally linked to the vaccines in question "accords better with facts of the case and the impressions of the treating physicians than any alternative theories." *Id.*

3. Dr. Sundel's Second Supplemental Expert Report

Dr. Sundel authored his second supplemental report on February 5, 2016. Pet'r's Ex. 24. In his report, Dr. Sundel reiterated his opinion that A.F.'s sJIA was caused by the aluminum adjuvant found in the DTaP and IP vaccines she received, and that molecular mimicry was not the likely process involved. *Id.* at 3, 5.

Dr. Sundel reaffirmed his conclusion that the short time interval between vaccination and disease onset is appropriate. He argued that "[a]lthough the pathophysiology of juvenile arthritis is still not understood," there is greater consensus that sJIA is an autoinflammatory disorder that is driven by the innate immune response. *Id.* at 2. He explained that "[a]utoinflammatory disorders are distinct from autoimmune diseases [because] [t]hey involve evolutionarily older and less adaptable methods of recognizing pathogens . . . rather than the infinitely mutable lymphocyte antigen receptors of the adaptive immune system." *Id.* Because these innate responses depend on "preformed mechanisms," he explained, they "typically occur more rapidly than adaptive responses . . . ." *Id.* Dr. Sundel stated that "[t]his is consistent with the rapidity of onset of Alexa's symptoms" post vaccination, which would rule out molecular mimicry as a possible causation mechanism. *Id.*

B. Petitioner's Expert, Michael Gurish, Ph.D.

Dr. Gurish received a Bachelor of Science in Biology and a Bachelor of Arts in Chemistry from the University of California at Irvine. Pet'r's Ex. 30 at 3, ECF No. 82-4. He also received a Doctor of Philosophy in Experimental Pathology (Immunology) from the University of Utah. *Id.* Dr. Gurish is an associate immunochemist at Brigham and Women's Hospital in Boston, MA. *Id.* at 2; Tr. 95:18–21. He is also an associate professor of medicine at Harvard Medical School, where he focuses on lymphocyte subsets in human rheumatic disease. *Id.* Dr. Gurish undertook two post-doctoral fellowships: he studied the regulation of humoral immunity at Brandeis University in Waltham, MA, and the molecular immunology of mast cells at Brigham and Women's Hospital and Harvard Medical School in Boston, MA. Pet'r's Ex. 30

[33] S. Cerpa-Cruz et al., *Adverse Events Following Immunization with Vaccines Containing Adjuvants*. IMMUNOL. RESEARCH 2013;56(2–3):299–303.

at 3. He is a member of the American Association of Science and the American Association of Immunologists, and he has authored more than one hundred publications, including articles on the cellular link between autoantibodies and inflammatory arthritis and the contribution of mast cells to the initiation of autoantibody-mediated arthritis. *Id.* at 3, 8–15. Although Petitioner did not move to admit Dr. Gurish as an expert in the field of immunology, he provided opinion testimony in that area. *See* Tr. 94:12–123:15.

Dr. Gurish submitted one expert report in this case. Pet'r's Ex. 29, ECF No. 76-1.

1. Dr. Gurish's Expert Report

Dr. Gurish submitted his expert report on February 13, 2017. Pet'r's Ex. 29. In his report, Dr. Gurish provided a more in-depth introduction to the immune system. Dr. Gurish explained that the innate immune system is the first responder to any potential pathogens by "eliminat[ing] components that appear different from what is normally present." *Id.* at 2. The innate system "then drives a more pathogen-specific response by stimulating lymphocytes, the T cells and B cells that compose the adaptive immune response." *Id.* He also wrote that all immune responses are "highly regulated and under constant surveillance" because they "can be damaging to the host if not contained." *Id.* He explained that any "[l]oss of specificity in the components that are targeted by the immune response can lead to autoimmunity[.]" *Id.*

Dr. Gurish agreed with Dr. Sundel that the medical community has come to distinguish between autoimmune and autoinflammatory response. *Id.* at 3. If the immune system dysfunction involves "the adaptive arm [of the immune system] and effector functions of T and or B cells[,]" it is referred to as autoimmune. *Id.* Conversely, a condition is autoinflammatory if "the response principally involves innate cells, such as macrophages[,] as the effector cells[.]" *Id.* Dr. Gurish stated that "[i]t is unlikely . . . that any reaction is exclusively an activation of one or the other arm of the immune response" due to the overlapping interactions between the two. *Id.* He noted, however, that "most cases of sJIA do not appear to be principally driven by the adaptive arm of the immune system" because the immune system's "response is dominated by macrophages[.]" *Id.* at 4 (citing Pet'r's Ex. 29, Tab F,[34] ECF No. 107-8; Pet'r's Ex. 23, Tab A;[35] Pet'r's Ex. 29, Tab D,[36] ECF No. 107-6).

Dr. Gurish wrote that sJIA has a "genetic association with a particular human [major histocompatibility complex ("MHC")] Class II molecule.[37]" *Id.* at 4 (citing Pet'r's Ex. 29, Tab

[34] C. Macaubas et al., *Distribution of Circulating Cells in Systemic Juvenile Idiopathic Arthritis across Disease Activity States*. CLINICAL IMMUNOL, 2010;134(2):206.
[35] Correll & Binstadt, *supra* note 25.
[36] P.A. Nigrovic, *Autoinflammation and Autoimmunity in Systemic Juvenile Idiopathic Arthritis*. Proceedings of the National Academy of Sciences of the United States of America, 2015;112(52):15785–86.
[37] MHC molecules "are heterodimeric cell surface receptors that function to present antigen peptide fragments to T cells responsible for cell-mediated immune responses." MHC Class II molecules "present exogenously derived antigenic peptides . . . to helper T cells." *MHC Class II, Alpha/Beta Chain, N-Terminal*, INTERPRO, http://www.ebi.ac.uk/interpro/ entry/IPR014745 (last visited May 30, 2019).

G,[38] ECF No. 107-9). He explained that MHC Class II molecules direct antigens to lymphocytes. *Id.* at 3. Because MHC Class II molecules vary from individual to individual, Dr. Gurish concluded that sJIA has a genetic component. *Id.* at 3–4. Additionally, Dr. Gurish noted that "alum has been shown to activate macrophages via the activation of and subsequent release of the NLRP3 inflammasome[39] and the polymerized downstream adapter molecule, ASC.[40]" *Id.* at 4. He explained that the ASC and NLRP3 can leave their originating cell and activate other macrophages, which "can lead to systemic macrophage activation." *Id.* Dr. Gurish conceded that it is unknown "whether this is the result of direct activation of the inflammasome by the aluminum compounds, or . . . the result of cell damage caused by the vaccination that leads to the release of activating damage-associated molecular patterns . . . that in turn activate the inflammasome within the innate cells[.]" *Id.* He nonetheless argued that "the end result of using [aluminum] adjuvant is activation of the innate cells, and the subsequent elaboration of cytokines such as IL-1 and IL-6," which are "two of the most important mediators of sJIA." *Id.* Dr. Gurish therefore concluded that "a recent immunization with a macrophage activating agent . . . can lead to systemic distribution of activating components and subsequently, the appearance of over[-]activated macrophages implicating the former in the production of the latter." *Id.* at 4–5.

Dr. Gurish further elaborated on Dr. Sundel's causation theory. *Id.* at 5. Dr. Gurish wrote that A.F.'s immune system was in flux following her treatment for an ear infection and noted two "critical factors" that show that the vaccination was the precipitating event for developing sJIA. *Id.* The first factor involves the time frame, because the innate immune response is activated within hours to days of exposure. *Id.* Dr. Gurish noted that A.F. began experiencing symptoms two to four days after vaccination, which he argues matches the results found in a study by Luján et al.,[41] which showed that the acute phase of the ASIA syndrome in commercial sheep occurred two to six days after "repetitive inoculation [with] aluminum-containing adjuvants[.]" *Id.* (citing Pet'r's Ex. 29, Tab J at 1, ECF No. 108-3). The second factor is that aluminum is known to activate "innate cells, in particular macrophages, via

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[38] M.J. Ombrello et al., *HLA-DRB1*11 and Variants of the MHC Class II Locus Are Strong Risk Factors for Systemic Juvenile Idiopathic Arthritis*. Proceedings of the National Academy of Sciences of the United States of America, 2015;112(52):15970–75.

[39] The NOD-like receptor pyrin containing domain 3 ("NLRP3") inflammasome "associates with Caspase-1 to form an inflammasome complex[, which] regulates cleavage of pro-inflammatory cytokines like IL-1β, IL-18 and IL-33 into their active forms, thereby activating multiple inflammatory processes." *See* Pet'r's Ex. 29, Tab K at 3, ECF No. 108-4, H. Bagavant et al., *Alum, an Aluminum-based Adjuvant, Induces Sjögren's Syndrome-like Disorder in Mice*. CLIN. AND EXPER. RHEUM. 2014;32(2):251–55. Caspase-1 is defined as "a group of cysteine endopeptidases that cleave proteins on the C-terminal side of aspartic acid residues as one of the final steps in apoptosis." *Dorland's* at 301.

[40] ASC stands for apoptosis-associated Speck-like protein with a caspase recruitment domain. It is an adaptor protein that "contains several . . . interaction domains so that it can act as a connector for interaction between molecules and facilitate [the] activation of pathways after receptors have been activated." *Dorland's* at 1531. "Inflammasome complexes are composed of a sensor protein connected to caspase-1, an interaction that in most cases requires the adaptor ASC." *See* Pet'r's Ex. 29, Tab H at 2, ECF No. 108-1, *A. Baroja-Mazo* et al., *The NLRP3 Inflammasome Is Released as a Particulate Danger Signal that Amplifies the Inflammatory Response*. NATURE IMMUNOL., 2014;15(8):738–48.

[41] L. Luján et al., *Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA Syndrome) in Commercial Sheep*. IMMUNOL. RESEARCH, 2013;56(2):317–24.

inflammasome activation," which leads to sJIA. *Id.* (citing Pet'r's Ex. 24, Tab I,[42] ECF No. 51-1). Dr. Gurish also wrote that there is evidence that although an immune response may be localized, "the response is really systemic even though it focuses at the site of the infection" because "immune cells can reenter the blood stream and traffic to other places in the body, especially to the site of the infection." *Id.* at 7. Dr. Gurish noted that the study by Luján et al. showed macrophages in the brain of sheep containing "white crystalline material," which shows that a substance such as aluminum could "become systemically dispersed." *Id.* Dr. Gurish concluded that although we do not know "what is driving the systemic innate response in [sJIA,]" the "various factors within this case" indicate that A.F.'s condition was caused by the DTaP vaccine. *Id.* at 7–8.

C. Respondent's Expert,[43] Dr. Carlos Rose, M.D., C.I.P.

Dr. Rose is a board-certified pediatric rheumatologist. Resp't's Ex. L at 3, ECF No. 101-1; Tr. 139:8–19. He received his medical degree from the University of Buenos Aires, Argentina, in 1977. Resp't's Ex. L at 1. Dr. Rose's post-doctoral training includes one year spent as a pediatric resident at the Medical Center of Delaware in Newark, DE, and two years spent as a rheumatology fellow at the National Institute of Rehabilitation, Rheumatology Division, in Buenos Aires, Argentina. Resp't's Ex. L at 4–5. He was also a pediatric rheumatology fellow for one year at the Children's Hospital of Philadelphia in Philadelphia, PA, and for two years at the Alfred I. duPont Institute in Wilmington, DE. *Id.*

Dr. Rose's clinical experience includes almost thirty years as staff physician and head of the division of rheumatology at the Nemours/Alfred I. duPont Hospital for Children in Wilmington, DE. *Id.*; Tr. 139:12–14, 139:23–140:3. Currently, he is a staff physician, researcher, and educator at the same institution, where he runs three half-day clinics per week and chairs the Institutional Review Board. Tr. 139:14–16, 140:10–11. In addition to his clinical experience, Dr. Rose is a professor of pediatrics at Thomas Jefferson University. Resp't's Ex. L at 6; Tr. 140:3–5. He has authored more than one hundred and twenty publications, including articles on juvenile idiopathic rheumatoid arthritis. Resp't's Ex. L at 6, 13–22; Tr. 139:18–22. Dr. Rose was admitted to testify as an expert in the field of pediatric rheumatology. Tr. 141:1–4.

Dr. Rose submitted one expert report and one supplemental report in this case. Resp't's Ex. A, ECF No. 32-1; Resp't's Ex. G, ECF No. 45-1.

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[42] P. He et al., *Advances in Aluminum Hydroxide-based Adjuvant Research and its Mechanism*. HUMAN VACCINES & IMMUNOTHERAP. 2015;11(2):477–88.

[43] In addition to the reports of Dr. Rose and Dr. Whitton, Respondent filed a white paper authored by Dr. Edward Cetaruk, which addressed the causation theory of ASIA. ECF No. 45-2. Dr. Cetaruk's report "wasn't submitted specific to this case[]" and, by not testifying, he did not provide context or rebuttal to Petitioner's arguments. *See* Tr. 326:11–327:3. Furthermore, Petitioner and the undersigned did not have the opportunity to cross-examine the expert. For these reasons, the undersigned gave less weight to his report in deciding this case.

1. Dr. Rose's Expert Report

Dr. Rose submitted his expert report on January 13, 2014, in response to Dr. Sundel's first expert report. Resp't's Ex. A. In his report, Dr. Rose primarily discussed the pathogenesis of sJIA. He wrote that A.F. had had no similar reaction to all previous vaccinations she had received, and her symptoms closely followed her ear infection. Resp't's Ex. A at 16. He posited that it is therefore more likely than not that A.F.'s sJIA was caused by a viral infection rather than the vaccines in question. *Id.*

Dr. Rose concurred with A.F.'s diagnosis of sJIA but disagreed that there was an "absence of alternative explanations." *Id.* at 7. He wrote that the vaccines were "not the only event preceding the onset of [A.F.'s] clinical disease." *Id.* at 8. Dr. Rose argued that a possible viral infection A.F. experienced at the end of March 2009 and the ear infection she had eleven days prior to the vaccination must also be considered as triggering factors. He explained that "[t]he rash of systemic JIA is more commonly faint and many times not even noticed by the patient or the parent." *Id.* at 7. By contrast, Dr. Rose noted that the purpuric rash A.F. had on March 27, 2009, "is unusual in [sJIA] except when the presentation of [sJIA] coincides with an episode of [MAS]." *Id.* During testimony, he also clarified that "a significant component of that . . . purpura[] is not seen in systemic JIA." Tr. 162:10–12. Dr. Rose also argued that because A.F.'s laboratory tests were negative for MAS on March 27, 2009, the purpuric rash could not have been a sign of sJIA at that point but of a viral infection. *Id.* He also noted that "[t]he lifetime risk of developing clinical MAS for a child with s[]JIA is about [ten percent] and of subclinical MAS perhaps [thirty to forty percent]." *Id.* at 12. He therefore argued that there is an "unquestionable link" between sJIA and MAS, with "some authors believ[ing] that the pathways of MAS could be a core mechanism for all s[]JIA." *Id.* at 12–13 (emphasis in original).

Dr. Rose stated that it is difficult to determine the environmental triggers that cause a rheumatic disease. *Id.* at 11. He explained that the onset of sJIA "is bound to be temporally associated with a multitude of events, all with more or less biological plausibility to cause/trigger" it. *Id.* He also noted that "[c]hildren suffer an average of [eight] mild infections a year and undergo multiple vaccinations during the period in which [sJIA] may be diagnosed." *Id.* In A.F.'s case, an ear infection was present, as was the 'possibility of a[viral] infection concurrent with or preceding the onset of her" disease. *Id.* Dr. Rose argued that A.F.'s sJIA was more likely than not caused by a combination of these factors and not the vaccines. *Id.*

Dr. Rose agreed with Dr. Sundel that sJIA is an autoinflammatory disease. *Id.* at 12. He explained that unlike autoimmune diseases, autoinflammatory diseases involve the presence of antibodies in the serum. *Id.* He also agreed that autoinflammatory diseases are linked to a dysfunction in the innate immune system, whereas autoimmune diseases "are likely linked to aberrations of the adaptive immunity." *Id.* He did note that although both systems are constantly at play, "the diseases resulting from malfunctioning of each of them are . . . differentiable." *Id.* This is because the innate immune system is designed to have the same rapid and predictable response to any antigen, whereas the adaptive immune system's response depends on knowledge gained from "previous exposure [to a certain antigen] and genetic make-up." *Id.* at 12–13.

Dr. Rose stated that there is a genetic link to sJIA; specifically, that it is "likely the result of polymorphisms in genes of the 'cytolysis pathway.'"[44] *Id.* at 16. He explained that the actors of the cytolysis pathway are linked to the innate immune system, which "remains 'static' throughout our lifespan in terms of recognition and response" to antigens. *Id.* at 16–17. Dr. Rose therefore argued that A.F.'s polymorphic genes would have had the same "MAS-like or a JIA[-]like response anytime she was exposed to" a vaccine containing aluminum adjuvant. *Id.* Because A.F. had never had a similar reaction with any previous vaccination and because "infections . . . are more likely to be associated with the onset of MAS [than vaccines]," he opined that the triggering factor of A.F.'s sJIA and MAS was more likely than not a viral infection. *Id.* at 17.

2. Dr. Rose's Supplemental Expert Report

Dr. Rose submitted his supplemental expert report on August 14, 2015, in response to Dr. Sundel's first supplemental expert report. Resp't's Ex. G. Dr. Rose reiterated his conclusion that A.F.'s sJIA was more likely than not caused by "her genetic make-up and the infectious events occurring prior to the onset of her symptoms[,]" and not the vaccines in question. *Id.* at 6. Although the cause of sJIA is unknown, he wrote, "viral triggers are well[]described for" MAS, particularly in people like A.F. who are genetically predisposed to both MAS and sJIA. *Id.* at 2. He explained that these viral triggers "are determinants of activation of the innate immune system which in turn leads to" sJIA and MAS in those susceptible to developing MAS. *Id.* at 2.

Dr. Rose also wrote that Dr. Sundel "suggest[ed] that the mechanism for Alexa's systemic JIA is somewhat in line with the so-called ASIA syndrome." *Id.* at 4. He argued, however, that there are several flaws regarding this causation theory. *Id.* at 2–6. First, he explained that the theory fails to address "the continued activation . . . of the innate immune system that would be required to explain a chronic disease like [sJIA]". *Id.* at 3. Second, he stated that ASIA's diagnostic criteria are inherently flawed, which renders them inapplicable to medical practice. *Id.* at 4. Specifically, none of the ASIA criteria, Dr. Rose explained, have been formally validated since the ASIA study was published in 2011. *Id.*

Lastly, Dr. Rose wrote that ASIA's major criteria can be easily met by the general population. *Id.* For instance, by the age of two months, most people have been vaccinated; the term "infectious stimuli" is a catch-all criterion that most people would satisfy; and because there is no specified interval between the introduction of an infectious stimulus and the onset of ASIA, "any condition at any age can theoretically be called ASIA if the individual . . . suffers from the 'typical' clinical manifestations." *Id.* Dr. Rose argued that ASIA is over-inclusive and "has not been substantiated by any reliable medical or scientific evidence." *Id.* It cannot, therefore, be used to explain the cause of A.F.'s sJIA. *Id.*

D. Respondent's Expert, Dr. J. Lindsay Whitton, M.D., Ph.D.

Dr. Whitton is an immunologist and he received his medical degree from the University of Glasgow, Scotland, in 1979. Resp't's Ex. M at 1–2, ECF No. 101-2. He also received his

[44] The cytolysis pathway refers to the "course . . . followed in the attainment of" the "dissolution or destruction of a cell by rupture of the cell membrane with loss of cytoplasm." *Dorland's* at 466, 1397.

Doctor of Philosophy in Herpesvirus Transcription from the same university in 1984. *Id.* Dr. Whitton's post-doctoral training includes three years spent as a research fellow on herpesvirus transcriptional control at the Medical Research Council in the United Kingdom and two years spent as a senior research fellow at the Department of Immunology of the Scripps Clinic in La Jolla, CA. *Id.* at 1. Dr. Whitton is currently a professor at the Department of Immunology and Microbiology of the Scripps Research Institute in La Jolla, CA, where he has been employed since 1989. *Id.* He is a member of the American Association of Pathologists, the American Association of Immunologists, the American Society of Virology, and the American Society of Microbiology. *Id.*

Dr. Whitton has been on the editorial board of several scientific journals, such as the Journal of Virology and Viral Immunology, and has authored close to two hundred peer-reviewed publications, including articles on vaccine-related research. *Id.* at 1, 4–14. Dr. Whitton has also been a speaker at several symposia and events organized by, *inter alia*, the World Health Organization, the European Union, and the Oregon Health & Science University. *Id.* at 16–18. Dr. Whitton is currently working with Prof. Joe McCormick and Dr. Mike Buchmeier to "construct[] Lassa virus[45] DNA vaccines to test in primates." *Id.* at 20. Dr. Whitton was admitted to testify as an expert in the field of immunology. Tr. 200:2–6.

Dr. Whitton submitted one expert report and two supplemental reports in this case. Resp't's Ex. I, ECF No. 45-3; Resp't's Ex. J, ECF No. 60-1; Resp't's Ex. K, ECF No. 86-1.

1. Dr. Whitton's Expert Report

Dr. Whitton submitted his expert report on August 14, 2015, in response to the causation theory proposed by Petitioner. Resp't's Ex. I. In view of Respondent's belief that Petitioner's experts' theory is based on ASIA, Dr. Whitton's report provides an overview of the ASIA theory and explains why it fails to link aluminum adjuvants and sJIA. *Id.* at 1. Dr. Whitton opined that because there is no scientific "evidence to support the notion that adjuvants in current use trigger any long-term systemic disease[,]" A.F.'s sJIA cannot be attributed to the vaccines she received. *Id.* at 16.

Dr. Whitton first elaborated on Dr. Rose's explanation of why a rapid response of the innate immune system could not have triggered A.F.'s sJIA. He explained that the innate immune system's response is "non-antigen specific." *Id.* It is "pre-programmed to mount a certain response," which "will be the same regardless of whether this is [its] . . . first encounter with a [specific] stimulus, or [its] tenth." *Id.* Conversely, the adaptive immune system is antigen specific and "can learn from experience[.]" *Id.* Thus, "its response to a second encounter with a specific antigen will be much more rapid, and biologically [] effective, than the first." *Id.* Dr. Whitton also stated that the responses of both the innate and the adaptive immune systems are not "entirely separate" but are instead "inextricably linked." *Id.* at 2.

Dr. Whitton then discussed the ASIA hypothesis in detail, articulating his main criticisms of this theory. He wrote that the authors of the ASIA study argue that the interval between

[45] Lassa virus is "an arenavirus . . . existing in several serologically distinct strains and distributed throughout West and Central Africa." *Dorland's* at 2063.

"'exposure to infection and the diagnosis of autoimmune disease' . . . can be as long as many years." *Id.* at 8. But no reliable data were offered to support this contention and, by extending the interval to years, he argued, it is "inevitable that all vaccinees will experience some episode of ill-health." *Id.* This, therefore, would mean that vaccination could be offered as the cause of any possible adverse event even years later. *Id.*

Dr. Whitton agreed with Dr. Rose that the diagnostic criteria of the ASIA hypothesis are flawed. Specifically, he noted that the "exposure to external stimuli" criterion is overbroad, while the absence of a temporal constraint "is inconsistent with well[]established immunological principles." *Id.* at 13. This is because it "runs counter to what we know of the immune response, which generally 'peaks' around [two] weeks after infection or vaccination, then declines over the next [one to two] weeks." *Id.* He also stated that the "appearance of 'typical' clinical manifestations" criterion is over inclusive because the symptoms listed are common and non-specific. *Id.*

Dr. Whitton also cast doubt upon ASIA's "removal of inciting agent induces improvement" criterion because infections that result in autoimmune diseases are "acute in nature" and therefore, "the inciting agent is [inherently] removed." *Id.* This runs counter to the ASIA study authors' contention that "acute infections . . . trigger long-term autoimmune disease." *Id.* Moreover, Dr. Whitton noted that the "appearance of . . . antibodies directed at the suspected adjuvant" criterion would not apply in this case because there are no aluminum-specific antibodies. *Id.* at 13–14.

Dr. Whitton concluded his criticism of the ASIA hypothesis by stating that it is an over-inclusive and "highly speculative" theory. *Id.* at 14. For instance, the "other clinical manifestations" criterion, he claimed, acts as a "fishing expedition" since any clinical manifestation can potentially be explained by ASIA. *Id.* Dr. Whitton also stated that "many of the statements made by [the ASIA study's authors] are not supported by cited scientific literature, and many of the papers that are cited appear to be extremely unreliable, or even irrelevant." *Id.*

2. Dr. Whitton's First Supplemental Expert Report

Dr. Whitton submitted his first supplemental expert report on August 4, 2016, in which he discussed the "biological plausibility" of the theory proposed by Dr. Sundel. Resp't's Ex. J at 1. Dr. Whitton opined that, based on the facts of this case and his knowledge of the function of the immune system, the evidence presented to support the theory "is extremely weak." *Id.* at 12.

In this report, Dr. Whitton explicitly stated that Petitioner's causation theory is "indistinguishable" from the ASIA hypothesis. *Id.* at 4. He argued that, like ASIA, Petitioner's causation theory fails for several reasons. First, Dr. Whitton wrote that one of the ASIA study authors, Dr. Yehuda Shoenfeld, has conceded that "every attempt for an epidemiological study has so far failed to deliver a connection" between autoimmune diseases and vaccines. *Id.* Additionally, Dr. Whitton noted that the Reeves et al.[46] article offered by Dr. Sundel to show that

[46] *See* Pet'r's Ex. 23, Tab F, ECF No. 105-9, W.H. Reeves et al., *Induction of Autoimmunity by Pristine and Other Naturally Occurring Hydrocarbons*. TRENDS IN IMMUNOL. 2009;30(9):455–64.

adjuvants "can trigger a variety of autoimmune diseases" is inapposite because the study involved pristane, which is not an adjuvant contained by any vaccine administered to humans and cannot therefore be equated to aluminum adjuvant. *Id.* at 5. Dr. Whitton agreed with Dr. Sundel that the Chen et al.[47] article shows that scientific evidence demonstrating a causation link between vaccines and autoimmune diseases remains "elusive." *Id.*

Dr. Whitton then criticized Dr. Sundel's reliance on the Cerpa-Cruz et al.[48] study to show a causal link between vaccines and autoimmune diseases. *Id.* at 6. He noted that the authors conceded that the study suffered from significant limitations, namely, its cross-sectional design; small population size; inherent selection bias; and, most importantly, the lack of a control group, without which there cannot be an appropriate comparison of the results. *Id.* These limitations, Dr. Whitton argued, "render the [study's] findings essentially meaningless." *Id.*

Dr. Whitton provided the results of controlled studies of adjuvanted vaccines to show that they have no deleterious effects on JIA. *Id.* at 7. He noted the study by Heijstek et al.[49] which found that "'[t]he bivalent HPV16/18 . . . is immunogenic and well tolerated in JIA patients.'" *Id.* He also stated that the safety of human papillomavirus vaccines in autoimmune diseases including JIA has been confirmed "in at least two other studies[,]" while the hepatitis B, meningococcus C, and adjuvanted influenza vaccines have also been found to be safe in patients with JIA. *Id.* (citing Resp't's Ex. J, Tab 4,[50] ECF No. 62-4; Resp't's Ex. J, Tab 5,[51] ECF No. 62-5; Resp't's Ex. J, Tab 6,[52] ECF No. 62-6; Resp't's Ex. J, Tab 7,[53] ECF No. 62-7; Resp't's Ex. J, Tab 8,[54] ECF No. 62-8). Dr. Whitton noted that "[t]he vaccines neither triggered JIA, nor [did they] exacerbate[] existing JIA[]" in any of the studies he reviewed. *Id.* Indeed, he continued, some vaccines are recommended in JIA patients because "the immune disruption [experienced by] JIA sufferers may render them more susceptible to the related pathogens." *Id.*

Dr. Whitton stated that A.F.'s sJIA could not have been triggered by the vaccines in question because A.F. had tolerated all previous vaccines. *Id.* at 8. Dr. Whitton agreed with Dr. Sundel that "adjuvants act, in general, by activating the innate immune system[.]" *Id.* He noted, however, that "unlike the adaptive immune system, the innate response does not have significant memory[]" because the innate immune system is designed to act rapidly. *Id.* He explained that "every time [the innate immune system] encounters a given stimulus . . . its response will be very

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[47] *See* Chen et al., *supra* note 28.
[48] *See* Cerpa-Cruz et al., *supra* note 33.
[49] *See* Resp't's Ex. J, Tab C, ECF No. 62-3, M.W. Heijstek et al., *Immunogenicity and Safety of the Bivalent HPV Vaccine in Female Patients with Juvenile Idiopathic Arthritis: A Prospective Controlled Observational Cohort Study*. ANN. RHEUM. DIS. 2014;73:1500–07.
[50] P. Pellegrino et al., *Immunogenicity and Safety of the Human Papillomavirus Vaccine in Patients with Autoimmune Diseases: A systematic review*. VACCINE 2015;33:3444–49.
[51] S. Esposito et al., *Immunogenicity, Safety and Tolerability of a Bivalent Human Papillomavirus Vaccine in Adolescents with Juvenile Idiopathic Arthritis*. EXPERT. REV. VACCINES 2014;13:1387–93.
[52] Y. Nerome et al., *The Safety and Effectiveness of HBV Vaccination in Patients with Juvenile Idiopathic Arthritis Controlled by Treatment*. MOD. RHEUMATOL. 2016;26:368–71.
[53] E. Zonneveld-Huijssoon et al., *Safety and Efficacy of Meningococcal C Vaccination in Juvenile Idiopathic Arthritis*. ARTHRITIS RHEUM. 2007;56:639–46.
[54] L. Dell'Era et al., *Immunogenicity, Safety and Tolerability of MF59-Adjuvanted Seasonal Influenza Vaccine in Children with Juvenile Idiopathic Arthritis*. VACCINE 2012;30:936–40.

similar." *Id.* Dr. Whitton therefore argued that without such memory, A.F.'s innate immune system could not have been "primed by previous vaccines." *Id.* Dr. Whitton also explained that sJIA requires a constant "'driver' of inflammation," which is inapposite to the innate immune system's response to an adjuvant, which is local and short lived. *Id.*

Dr. Whitton argued that A.F.'s sJIA was triggered by her previous ear infection, whose "[b]acterial DNA is a strong stimulator of the innate immune response . . . and abundant DNA is made during a bacterial infection." *Id.* at 11. The purpuric rash A.F. also had on March 27, 2009, "might have been reflective of an undiagnosed viral infection" since such rash is not a sign of JIA or MAS. *Id.* Dr. Whitton concluded that A.F.'s condition was more likely than not caused by a viral infection close in time to the vaccine administration. *Id.* at 11–12.

3. Dr. Whitton's Second Supplemental Expert Report

Dr. Whitton submitted his second supplemental expert report on May 30, 2017, in response to Dr. Gurish's expert report. Resp't's Ex. K. In this report, Dr. Whitton reiterated his critique of the ASIA hypothesis. *Id.* at 1–3. He also reiterated his conclusion that a viral infection was the more likely trigger for A.F.'s sJIA rather than the vaccines she received. *Id.* at 13–15.

Dr. Whitton discussed in detail all the studies submitted by Dr. Gurish to support Petitioner's theory that an adjuvanted vaccine was the likely cause of A.F.'s sJIA. He first discussed the Luján et al. study.[55] He argued that the authors "appear to have reached their conclusion before starting their analyses," namely, that the ovine ASIA syndrome observed in the study sheep was "related to adjuvants within the vaccines." *Id.* at 4. Instead, Dr. Whitton argued that given the high doses of aluminum to which the sheep had been exposed over a prolonged period, "many of the findings can be attributed to aluminum intoxication." *Id.* at 5. Dr. Whitton also noted that the study was "extremely poorly . . . controlled" for three reasons: (1) it failed to include a group that received only the adjuvant so any result comparison would be rendered meaningless; (2) the group size of three sheep each was very small; and (3) the sheep "received a smorgasbord of 14 vaccines" which made it "impossible to identify the responsible vaccine component (if any)." *Id.* at 5–7. Finally, Dr. Whitton stated that the study is inapplicable because, unlike in A.F.'s case, "no acute disease was observed." *Id.* at 6.

Dr. Whitton also noted weaknesses in the study by Bagavant et al.,[56] which Dr. Gurish offered to support the idea that "vaccination with alum can indeed trigger an autoimmune response." *Id.* at 7. Dr. Whitton wrote that the concentration of aluminum administered to the study mice was high. *Id.* at 8. Indeed, he noted, "when corrected for body weight, these mice appear to have been given around . . . [nine hundred and twenty-four thousand times the dose that is given in a human vaccine." *Id.* "[G]iven the absence of any clear sign of autoimmunity[,]" aluminum toxicity is "an adequate explanation" for the study findings rather than the authors' conclusion that the vaccines were to blame. *Id.* at 8–9. Additionally, Dr. Whitton argued that the various routes of administration employed by the study authors do not match the intramuscular route employed when administering vaccines to humans. *Id.* at 8. He

[55] *See* Luján et al., *supra* note 41.
[56] *See* Bagavant et al., *supra* note 39.

agreed with Dr. Gurish in his expert report, that based on the administration route used, "[t]he bio-distribution will be different." *Id.*; *see also* Pet'r's Ex. 29 at 8 (noting that "a basic tenet of immunology is that [the] route of exposure is critical to determining the ultimate reaction.").

Dr. Whitton concluded by rebutting Dr. Gurish's criticisms of Dr. Whitton's previous expert reports. He noted that Dr. Gurish agreed "that an ongoing driver is necessary" in autoinflammatory disorders like sJIA. *Id.* at 12–13. This, he argued, puts it at odds with Dr. Gurish's contention that aluminum adjuvant triggered A.F.'s sJIA because the effects of aluminum are local and short lived. *Id.* Dr. Whitton also argued that the "innate memory" proposed by Dr. Gurish to explain why A.F. had no response to previous vaccinations fails for two reasons. *Id.* at 13. First, he noted that studies on innate memory "suggest that only [two to three] exposures are required to reach a maximal level[,]" which is much lower than the seventeen previous vaccines A.F. had received, "many of which contained alum[.]" *Id.* at 13. Second, he explained that the long-term effects of innate memory last days to weeks after vaccination, whereas here A.F.'s previous DTaP vaccination was on April 10, 2006, i.e., almost three years previously. *Id.* This time interval, he argued, "far exceed[s] the known duration of 'innate training.'" *Id.*

E. Expert Testimony

1. Dr. Sundel's Testimony

Dr. Sundel described sJIA as a "multifactorial" condition that requires "a susceptive area, presumably genetic," and "numerous triggers that seem to be able to push a child over," usually "low-grade inflammation that is controlled[.]" Tr. 27:10–18. He explained that at some point "something increases the amount of inflammation in the child," who cannot control it, and "it explodes into a case of systemic JIA." Tr. 27:18–21. Dr. Sundel noted that it was "a challenge to diagnose" A.F.'s condition because "[t]here is not a single clinical manifestation, nor a single laboratory test, nor a single imaging study that can make the diagnosis." Tr. 19:24–20:5. He explained that A.F. "had high markers of inflammation" and "specific tests for specific diseases were all negative." Tr. 19:22–20:1. He therefore argued that A.F.'s overall clinical presentation and certain medical expertise were required to "rul[e] out all of the other possibilities" to properly diagnose her with sJIA. Tr. 20:5–7.

Dr. Sundel testified that we know A.F. was unable to control her inflammation because of the presence of MAS, which he described as a "cytokine storm." Tr. 29:24–30:6. He explained that during a cytokine storm "so many arms of the immune system are activated simultaneously, [and] the body cannot handle that." Tr. 30:8–10. He noted that when a child, like A.F., is genetically predisposed, the aluminum adjuvant may stimulate the immune system to such a degree as to enhance its response, thus leading to a cytokine storm. Tr. 34:21–35:4, 38:25–39:6, 39:19–40:8. Dr. Sundel also argued that the presence of MAS in A.F. is "further evidence that she has systemic JIA, since [MAS is] so prevalent in that disease more than any other disease." Tr. 41:23–42:3.

Dr. Sundel noted that although A.F. was "genetically susceptible to systemic arthritis" that was not enough to trigger the disease. Tr. 43:11–15. Rather, he argued, A.F.'s

inflammasomes and the rest of her innate immune system were triggered by a "concatenation" of factors to cause her to develop sJIA. Tr. 43:3–9, 45:18–46:2. Dr. Sundel likened A.F.'s condition to a "bubbling pot" created by a combination of her genetic predisposition and a variety of environmental factors, with the vaccines being "a brick [thrown] into [the pot] and it overflowed." Tr. 53:9–25. He also equated the occurrence of A.F.'s condition to wildfires. Tr. 42:15–43:9. Although factors leading to wildfires, such as dry conditions or strong winds, can be present in many different circumstances, wildfires happen only once the right conditions are met. *Id.* In the same way, A.F. only developed sJIA due to "changes in her body:" (1) "her diet was different [so] she had different bacteria in her gut[;]" (2) antibodies she had produced in response to her earlier ear infection were present in her body; and (3) the amoxicillin she had taken had "change[d] the bacteria in her intestine." Tr. 43:18–25. Ultimately, Dr. Sundel argued that DTaP vaccine was "the final blow" because the aluminum adjuvant "stimulated both [A.F.'s] innate and adaptive immune system," resulting in the cytokine storm. Tr. 44:2–9. Dr. Sundel stated that, similar to a wildfire, the cause of a rare occurrence like A.F.'s condition could only be discerned in retrospect due to the multivariate nature of the cause. *Id.* at 44:10–17.

On cross-examination, Dr. Sundel stated that he believes aluminum triggered A.F.'s innate immune system because the data concerning aluminum show "that it . . . has this type of an effect on the inflammasome and on the innate immune system." Tr. 58:21–24. This immune response is "normal" and occurs in any vaccine with aluminum. Tr. at 56:12–18. Dr. Sundel noted that in A.F.'s case "the difference . . . was that she could not control" the innate system's inflammatory response. Tr. 59:9–10. When asked how much aluminum a person ingests daily, Dr. Sundel replied that he did not know and reiterated that his "multi-hit hypothesis [is] that it took a lot of inflammation to overwhelm [A.F.'s] controls and cause her to have a chronic inflammatory disorder like systemic arthritis." Tr. 78:1–12, 78:20–23. Finally, Dr. Sundel disagreed that his causation theory of A.F.'s condition is analogous to the ASIA theory because ASIA is "an overly broad generalization of what happens with vaccines[.]" Tr. 72:4–9. In fact, Dr. Sundel rejected ASIA as "too broad for a theory that will have any use in clinical medicine, or even in the legal system." Tr. 84:20–22. Instead, he argued that his causation theory is similar to "the more specific studies of things such as alum and IL-18" because, unlike ASIA, those do not have the potential of encompassing almost all types of signs, symptoms, and sequelae. Tr. 74:1–6.

The undersigned asked Dr. Sundel how he can base his theory of ASIA on the pathogenesis of JIA when the pathogenesis is unknown. Tr. 86:1–2. Dr. Sundel explained that although the pathogenesis is unknown, what we do know about the "development and manifestations of [JIA] on a cellular level" is that it is an autoinflammatory disease where inflammasomes, interferon, Interleukin-1 ("IL-1"),[57] Interleukin-6 ("IL-6"),[58] and Interleukin-18

[57] Interleukin-1 is a "predominately macrophage-produced [cytokine] that mediates the host inflammatory response in innate immunity . . . . At low concentrations, [it] principally acts to mediate local inflammation," whereas "at high concentrations [it] enters the blood stream and acts as an endocrine hormone." *Dorland's* at 949.

[58] Interleukin-6 is a "lymphokine produced by antigen- or mitogen-activated T cells, fibroblasts, macrophages, and adipose and other cells that serves as a differentiation factor for B cells and thymocytes and stimulates immunoglobulin production by B cells; it also induces hepatocytes to synthesize various plasma proteins involved in the acute phase response." *Dorland's* at 949.

("IL-18")[59] play an important role. Tr. 89:3–10. The undersigned then asked Dr. Sundel how he distinguishes between a causal relationship and a byproduct with respect to IL-6 and IL-18. Tr. 86:12–14. Dr. Sundel stated that there is no evidence of a causal relationship due to a lack of studies performed on such a rare disease. Tr. 86:18–87:2. Dr. Sundel also clarified that he does not agree with ASIA because he does not know whether causation can be limited to the adjuvant. Tr. 88:10–13. Dr. Sundel then explained the importance of the pre-vaccine ear infection. Tr. 88:16–90:17. Dr. Sundel stated that the ear infection activated A.F.'s innate and adaptive immune systems and, although there were no signs of infection, the immune response was still active and elevated. *Id.* at 88:21–90:7. In that context, he continued, the aluminum adjuvant further activated A.F.'s immune system to such a degree that it "overwhelm[ed her body's] control mechanisms[,]" resulting in sJIA. Tr. 89:10–17. Under re-direct examination, Dr. Sundel stated that the incidence rate for sJIA in the United States is 0.5 per one hundred thousand children, which classifies it as a "orphan disease" by the federal government, i.e., rare. Tr. 90:16–91:8. Because the disease is rare, it would be very difficult to study in children. Tr. 90:13–17.

2. Dr. Gurish's Testimony

Dr. Gurish agreed with Dr. Sundel and distanced himself from the ASIA hypothesis during testimony. Tr. at 127:22–128:7. Dr. Gurish stated that although "the ASIA hypothesis is intriguing in the sense that someone is trying to understand these adverse events on a very global scale . . . it's hard to make predications based on this global hypothesis . . . ." *Id.* Dr. Gurish, also agreed with Dr. Sundel's characterization of a causal theory similar to a wildfire. Tr. 112:20–25, 130:6–11.

During his testimony, Dr. Gurish stated that aluminum has the ability to trigger the type of immune system reaction that, if uncontrolled, results in sJIA. Tr. 105:5–106:15. Dr. Gurish explained that aluminum "activates . . . macrophage[s] and induces the formation of inflammasomes." Tr. 105:24–106:2. Once this occurs, inflammasomes produce cytokines, which result in "increased . . . phagocytosis.[60]" Tr. 106:9–11. Dr. Gurish then cited to the studies by Luján et al.[61] and Bagavant et al.[62] as evidence that aluminum activates the innate immune system. *Id.* at 108:17–112:9. Dr. Gurish clarified that the mice used in the Bagavant et al. study were genetically susceptible to develop Sjögren's syndrome, and he would view the aluminum introduced in the study as a trigger for the development of this condition. Tr. 109:21–110:10, 111:2–22. Dr. Gurish also agreed with Dr. Sundel that A.F.'s prior ear infection and

[59] Interleukin-18 is a cytokine whose serum "levels are increased in active s-JIA. Thus, serum IL-18 levels are increasingly used as a biomarker for s-JIA diagnosis and of its therapeutic response in s-JIA . . . . Serum IL-18 levels are even further increased in patients with s-JIA-related MAS . . . ." *See* Pet'r's Ex. 24, Tab O at 2, ECF No. 107-2, M. Shimizu M et al., *Interleukin-18 for Predicting the Development of Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis*. CLINICAL IMMUNOL. 2015;160:277–81.

[60] Phagocytosis is the "process by which certain living cells called phagocytes ingest or engulf other cells or particles." ENCYC. BRITTANICA, https://www.britannica.com/science/phagocytosis (last visited May 30, 2019).

[61] *See* Luján et al., *supra* note 41.

[62] *See* Bagavant et al., *supra* note 39.

antibiotic treatment were contributing factors to A.F. developing sJIA rather than the cause. Tr. 113:12–114:15.

Dr. Gurish reiterated his argument that aluminum can move throughout the immune system after vaccination via aluminum-containing translocating macrophages. Tr. 106:25–107:20. Dr. Gurish cited to the studies by Khan et al.[63] and Flarend et al.[64] to show that aluminum has been found to translocate in animals. Tr. 116:22–118:12, 120:12–121:12. Specifically, he stated that the Khan et al. study showed that aluminum can translocate to the brain via macrophages, while the Flarend et al. article showed that aluminum that had been injected intramuscularly in rabbits was later found in the spleen and kidneys. *Id.*

In a similar fashion as Dr. Sundel, upon cross-examination, Dr. Gurish distanced himself from ASIA. He agreed with Dr. Sundel that although an "intriguing" theory, ASIA is too overbroad to use effectively. Tr. 127: 24–128:5. He also acknowledged the flaws in the Cerpa-Cruz et al.[65] study mentioned during Dr. Sundel's cross-examination. Tr. 126:19–127:18. He nevertheless found it to be "suggestive evidence" as a retrospective study despite the inherent design flaws. *Id.* The undersigned asked Dr. Gurish about whether he defined an adverse event following vaccination as an isolated incident or the result of a multifactorial culmination of events. Tr. 129:12–130:5. Dr. Gurish answered that "it is a multifactorial system that's come together in a negative fashion to produce this adverse event, but there are multiple factors that needed to come together at the right time to lead to the event." Tr. 130:6–11. Dr. Gurish also noted that it would be very difficult to design a study to test this hypothesis on humans because "we don't have a way of distinguishing all these different factors." Tr. 131:7–19. The undersigned asked whether, in a study based upon Dr. Sundel's hypothesis, one would have to work from one factor, i.e., the vaccine, and then "compare the other factors, as long as they all have the same adverse event," i.e., autoinflammation. Tr. 132:12–16. Dr. Gurish agreed, with the caveat that each individual in the study may present with a "subtly" or "dramatically different" form of the disease. Tr. 132:19–24.

3. Dr. Rose's Testimony

Dr. Rose testified that A.F.'s "two viral insults, one before the [sJIA], and one before the MAS[]" were the cause of her condition. Tr. 157:8–15. He first noted that A.F.'s two cell counts from the end of March 2009 are not consistent with A.F. having sJIA at that time. Tr. 148:7–11. He explained that A.F.'s cell count from March 24, 2009, "suggests a viral infection," while the one from March 26 is "typical . . . of a patient on steroids[, e.g., A.F.]" Tr. 147:10–13, 147:23–148:6. Dr. Rose argued that although we cannot know the exact onset of A.F.'s sJIA, her cell counts show that "beyond question [A.F.] was experiencing a viral insult[]" at the end of March 2009. Tr. 148:13–16.

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[63] Pet'r's Ex. 29, Tab M, ECF No. 108-6, Z. Khan et al., *Slow CCL2-dependent Translocation of Biopersistent Particles from Muscle to Brain*. BMC MEDICINE 2013;11(1):99.
[64] Pet'r's Ex. 29, Tab L, ECF No. 108-5, R. Flarend et al., *In Vivo Absorption of Aluminium-containing Vaccine Adjuvants Using 26Al*. VACCINE 1997;15.
[65] *See* Cerpa-Cruz et al., *supra* note 33.

Dr. Rose argued that by April 2009, A.F. was already suffering from "a garden-variety systemic onset JIA." Tr. 149:14–17. At that point, he explained, A.F. had her second viral infection in the form of a dry cough. Tr. 150:10–151:8. And, once again, he continued, she had "an abnormal response to a viral infection" with her erythrocyte sedimentation rate ("ESR")[66] rate normalizing, even though she had sJIA. *Id.* This time, however, A.F. developed MAS. Tr. 151:9–11. Dr. Rose explained that thirty to forty percent of sJIA patients have a lifetime risk of developing MAS, of whom "[ten] percent are clinically diagnosable and the other [twenty] or [thirty] are subclinical." Tr. 153:3–9. He then cited to the Ravelli et al.[67] study which showed that because patients with sJIA "have slightly abnormal variants of the[familial HLH] genes[,]" they are prone to developing MAS. Tr. 155:25–156:7. He explained, when gamma interferon is released as a response to a viral infection, it "activates the macrophages, and this activation persists . . more macrophages are recruited, more cytokines are released, and you enter this situation of the cytokine storm[.]" Tr. 156:8–23. Dr. Rose argued that this shows the important role viral infections play in an individual like A.F. who has sJIA and is genetically predisposed to developing MAS. Tr. 157:8–15.

Dr. Rose then testified that the aluminum-adjuvanted vaccine did not cause A.F.'s sJIA and MAS. He explained that a genetic cause is more plausible because aluminum is an environmental factor. Tr. 157:25–158:2. Environmental factors are more difficult to pinpoint because "they're very hard to control[] and . . . they're happening all the time [because] they are in the atmosphere." Tr. 158:2–5. In A.F.'s case, Dr. Rose argued, we already know A.F. was predisposed to sJIA and she suffered two viral infections. Tr. 158:6–22. He concluded that it is more likely than not that these were the causes of her sJIA and not the aluminum adjuvant in the DTaP vaccine. *Id.* Dr. Rose also noted that A.F. could not have had sJIA as early as March 2009 because she had no "abnormal response to th[e] vaccine[,]" e.g., fever, which would be evidence of "a clinical and relevant activation of the innate immune system." Tr. 160:1–13.

On cross-examination, Dr. Rose reiterated that A.F.'s fever, joint pain, rash, and elevated C-reactive protein ("CRP")[68] on March 24, 2009, were caused by a virus and not her sJIA. Tr. 162:3–15; 191:2–7. He explained that MAS "is overwhelmingly a post-viral phenomenon" and it is "highly suggestive of carrying [specific] genes that make [an individual] have an abnormal response to viral infections." Tr. 188:19–21. It is therefore more likely, he continued, that A.F.'s fever and rash at that time were caused by a virus. Tr. 188:21–189:1. Dr. Rose also noted that A.F.'s treating physicians at that time must have also thought that she had a viral infection because they kept on testing her for a virus. Tr. 162:18–22; 162:25–163:3. He explained that even though all the tests came back negative, doctors can only "test for the most common and the most likely that [they] have a test for." Tr. 163:9–14; 171:17–18. He also pointed out that

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[66] The ESR is "the rate at which erythrocytes precipitate out from a well[]mixed specimen of venous blood." The ESR "is increased in . . . active inflammatory disease." *Dorland's* at 1594.

[67] *See* Resp't's Ex. F, ECF No. 33-4, A. Ravelli et al., *Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment*, GENES AND IMMUNITY 2012;13:289–98.

[68] The CRP "is a blood test marker for inflammation in the body" that "is classified as an acute phase reactant, which means that its levels will rise in response to inflammation." *C-Reactive Protein CRP Test, Ranges, Symptoms, and Treatment*, MEDICINENET, https://www.medicine net.com/c-reactive_protein_test_crp/article.htm#what_is_c-reactive_protein_crp (last visited May 30, 2019).

A.F.'s normal white blood cell count coupled with an elevated ESR and CRP is "the result of a viral infection" that was perhaps associated with a vasculitis. Tr. 167:14–18. This would also explain why A.F. had purpura. Tr. 192:17–193:7.

4. Dr. Whitton's Testimony

Dr. Whitton testified that although aluminum triggers the innate immune system, which produces cytokines, "the duration of that triggering is short." Tr. 202:1–4. He explained that triggering merely "limit[s] the number of . . . minor adverse effects that often occur after vaccination," the most common of which are "erythema, swelling or hardness of the skin, and pain and fever." Tr. 202:8–14. He also noted that these adverse effects are "short-lived[; t]hey occur usually within the first [twenty-four] to [forty-eight] hours and they dissipate fairly rapidly thereafter." Tr. 202:15–20.

Dr. Whitton stated that there is no evidence that the "tiny" amount of aluminum distributed in the body is pathogenic or disease causing. Tr. 203:19–20. In support, he cited to the 2007 study by Didierlaurent et al.,[69] which showed that the effects of aluminum are limited temporally and spatially. Tr. 204:1–6. He also noted several differences between aluminum adjuvants and viruses in terms of their impact on the innate immune system. First, unlike adjuvants which cannot replicate, a virus is "a highly replicating organism who[se] nucleic acid components multiply into the certainly many, many millions." Tr. 209:16–22. Viruses, he explained, can therefore "trigger a variety of different sensors[,]" thus resulting in a "profound innate immune response[.]" *Id.* Moreover, unlike adjuvants whose amount does not increase in the body, "the amount of viral nucleic acid, and therefore the amount of material capable of . . . ongoing stimulation of the innate immune system, is rising for several days." Tr. 209:22–210:10. He explained that this results in a more prolonged response. Tr. 209:22–23.

Dr. Whitton also testified that aluminum adjuvants could not cause sJIA because their effect on the innate immune system diminishes as they are eliminated by the body. Tr. 207:1–7. On the other hand, he argued that viral infections are a more likely cause because sJIA requires "a persistent driver [that continues to replicate in order] to evolve and clinically manifest." Tr. Tr. 209:22–210:10; 211:10–12; 214:4–6. Because aluminum "adjuvant can't multiply[,]" it does not constitute a "persistent driver." *Id.* Dr. Whitton explained that in A.F.'s case, her genetic susceptibility "to developing hyper responses as a result of deficiency," will be "most strongly [triggered], without any question, [by a] virus infection." Tr. 213:7–13. He added that "alum has never been shown to cause macrophage activation syndrome." He therefore argued that the most likely cause of A.F.'s MAS and sJIA is a virus that cannot be shut down due to A.F.'s genetic susceptibility. Tr. 213:17–214:3.

On cross-examination, Dr. Whitton testified that he based his opinion that A.F.'s sJIA was the result of a viral infection on the inclusion of the phrase "viral syndrome" in A.F.'s medical records, the testimony from the other three experts, and his own knowledge of immunology. Tr. 217:21–25; 221:14–19. He explained that "of the two options, option one

[69] *See* Resp't's Exhibit J, Tab 19, ECF No. 63-9, A.M. Didierlaurent et al., *AS04, an Aluminum Salt- and TLR4 Agonist-Based Adjuvant System, Induces a Transient Localized Innate Immune Response Leading to Enhanced Adaptive Immunity*, THE JOURNAL OF IMMUNOL. 2009; 183: 6186–97.

being alum-triggered . . . sJIA and . . . MAS[] and option two being that a virus infection triggered it," a viral infection is "a plausible interpretation and more plausible than a reaction to alum because a reaction to alum should not be substantially different in somebody who is lacking cytotoxic activity[.]" Tr. 221:19–222:12. Dr. Whitton also noted that A.F.'s genetic deficiency in her cytotoxic activity "may have played a role in prolonging the innate immune response to viral nucleic acids which otherwise would have been cleared had that infection occurred in" people without said deficiency. Tr. 230:20–24.

IV. The Applicable Legal Standard

To receive compensation under the Vaccine Act, Petitioner must demonstrate either that: (1) A.F.'s injury is a "Table Injury" and therefore resulted from the receipt of a covered vaccine or vaccines within the time frame prescribed by the Vaccine Injury Table set forth at § 14, as amended by 42 C.F.R. § 100.3; or (2) A.F.'s injury is an "off-Table Injury," one not listed on the Table, that resulted from her receipt of a covered vaccine. *See* § 11(c)(1)(C); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1319–20 (Fed. Cir. 2006). Petitioner's claim that A.F.'s vaccines caused her injury does not fall within the Vaccine Table. Thus, it must be proven that her vaccines were the cause-in-fact of her injury.

To establish causation-in-fact, Petitioner must demonstrate by a preponderance of the evidence that the vaccines were the cause of A.F.'s injury. § 13(a)(1)(A). Petitioner is required to prove that the vaccines were "'not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Moberly*, 592 F.3d at 1321–22 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)). To do so, Petitioner must provide evidence demonstrating a logical sequence causally linking the vaccination and the injury. *Shyface*, 165 F.3d at 1352–53 (quoting *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992)). The vaccines received, however, need not be the predominant cause of the injury. *Shyface*, 165 F.3d at 1352. Rather, the vaccines "must be a substantial factor in bringing about the harm." *Id.*

In *Althen v. Sec'y of Health & Human Servs.*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278 (Fed. Cir. 2005). The *Althen* test requires a petitioner to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.* (internal citations omitted).

Specifically, under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question "can [the] vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004) *aff'd sub nom. Pafford ex rel. Pafford v. Sec'y of Dep't of Health & Human Servs.*, 64 Fed. Cl. 19 (2005), and *aff'd sub nom. Pafford v.*

Sec'y of Health & Human Servs., 451 F.3d 1352 (Fed. Cir. 2006). This may be accomplished in a number of ways. "Reliability and plausibility of . . . pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory, so as to render it credible." *Id.* Additionally, "epidemiological studies and an expert's experience, while not dispositive, lend significant credence to the claim of plausibility." *Id.* Medical literature published in respected medical journals is also persuasive. *Id.* "However, publication 'does *not* necessarily correlate with reliability,' because 'in some instances well-grounded but innovative theories will not have been published.'" *Id.* (quoting *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 593–94 (1993) (emphasis in original)). Furthermore, a petitioner is not required to present medical literature or epidemiological studies to prove her burden. *Grant*, 956 F.2d at 1149; *Andreu v. Sec'y Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). However, to the extent medical literature and epidemiological studies are provided, these are subject to critique by Respondent's experts, and the special master will consider them when deciding whether the petitioner has met her burden of proof.

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also, under *Althen's* second prong, prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1278. A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; the petitioner "must explain *how* and *why* the injury occurred." *Pafford*, 2004 WL 1717359, at *4 (emphasis in original) (internal citations omitted).

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. The special master cannot infer causation from temporal proximity alone. *See Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403–04 (Fed. Cl. 1991); *see also Grant*, 956 F.2d at 1148 ("'[T]he inoculation is not the cause of every event that occurs within the ten[-]day period. . . . Without more, this proximate temporal relationship will not support a finding of causation.'" (quoting *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983))).

Petitioners who demonstrate by a preponderance of the evidence that they suffered an injury caused by vaccination are entitled to compensation, unless Respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1386 (Fed. Cir. 2015) (citing *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008) (holding that it is not a petitioner's burden "to rule out possible alternative causes" (internal citations omitted))); *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994). Under the Vaccine Act, the government's burden is to prove by a preponderance of the evidence that a substantial factor unrelated to the vaccine caused the injury. 42 U.S.C. § 300aa–13(a)(1)(B). This is identical to the burden of proof a petitioner bears to establish his prima facie case. *Id.* § 300aa13 (a)(1)(A). The Federal Circuit has stated that "the standards that apply to a petitioner's proof of actual causation in fact in off-table cases should be the same as those that apply to the government's proof of alternative actual causation in fact." *Knudsen*, 35 F.3d at 549.

V. Discussion

A. Experts

Petitioner and Respondent both provided two experts, one each qualified to testify in the areas of rheumatology and immunology. Dr. Sundel, for Petitioner, and Dr. Rose, for Respondent, are board-certified pediatric rheumatologists. Dr. Sundel has impressive credentials with more than sixty relevant publications and experience treating over one hundred and fifty juvenile arthritis patients. Qualifications notwithstanding, Dr. Sundel's expertise was undercut by his vague and inconsistent causation theory. Dr. Sundel testified that "really it's confusing" and it "needs to be understood better, [but he] think[s] it is a reasonable hypothesis[.]" Tr. 85:14–15; 83:6–11. Dr. Sundel concluded that "[n]ew information on the role that aluminum adjuvants appear to play in the development of autoimmunity following vaccinations . . . accord well [with] the demographic, epidemiologic and chronologic characteristics of the events" that can result in vaccine-caused sJIA. Pet'r's Ex. 23 at 5. Despite this clear assertion that sJIA is an autoimmune syndrome induced by adjuvants, Dr. Sundel did not refer to his theory by the ASIA acronym well known in the program. In fact, during cross-examination, Dr. Sundel stated, "I'm not invoking ASIA at all. I don't think that's relevant." Tr. 60:23–24. Dr. Sundel's rejection of ASIA is contradicted by his filed medical literature. When asked for his "best evidence that an aluminum salt adjuvant can trigger pathologic inflammation[]" or another adverse event, Dr. Sundel referenced the Cerpa-Cruz et al.[70] study. Tr. 82:1–18. Cerpa-Cruz et al. is a study designed to test the ASIA theory. The authors wrote, "[o]ur results suggest that vaccines containing adjuvants may be associated with an increased risk of autoimmune/inflammatory adverse events following immunization." Pet'r's Ex. 23, Tab L at 4. If Dr. Sundel believes that ASIA is "too broad for a theory that will have any use in clinical medicine, or even in the legal system[,]" it is unclear why he would rely on papers by Dr. Shoenfeld, one of the leading proponents of ASIA, and Cerpa-Cruz et al., who set out to test the veracity of ASIA. Tr. 84:20–22; *see* Pet'r's Ex. 23, Tab D; Pet'r's Ex. 23, Tab L. Dr. Sundel praised Dr. Shoenfeld's work while acknowledging that it needs to be understood better. Tr. 83:2–10. He ultimately conceded, "[i]t's not proof, I acknowledge that." Tr. 83:10–11.

By contrast, during testimony, Dr. Rose expanded on the opinion he expressed in his reports, namely, that a viral infection, rather than the vaccines, caused A.F.'s sJIA. Dr. Rose believed that Dr. Sundel was asserting an ASIA-based theory. He briefly critiqued the ASIA theory but focused on how A.F.'s manifestations of sJIA and MAS were consistent with the more commonly seen viral-induced sJIA. Dr. Rose's application of his clinical knowledge of sJIA to A.F.'s case was persuasive evidence that he was able to recognize and explain what happened to her.

Dr. Gurish, Petitioner's immunochemist, is an acclaimed researcher and professor. Although he was not admitted to testify as an expert in immunology, Dr. Gurish exhibited his expertise in the area through his written report and testimony. He was less helpful, however, beyond providing a general overview of the immune system and responses. He agreed with Respondent's expert Dr. Whitton that the Cerpa-Cruz et al.[71] study was not without flaws. He

[70] *See* Cerpa-Cruz et al., *supra* note 33.
[71] *Id.*

also testified that he "would echo Dr. Sundel's opinion that while the ASIA hypothesis is intriguing . . . it also is disruptive . . . [and] it's hard to make predictions based on this global hypothesis." Tr. 127: 24–128:5. Dr. Gurish did not explain how he had narrowed Dr. Shoenfeld's ASIA theory. He did not explain away holes in the causation theory that relate to its vague symptoms or unspecific triggers. He was less persuasive for many of the same reasons as Dr. Sundel.

Dr. Whitton is a more persuasive immunology expert because he has had more than twenty years of experience as a professor of immunology, together with outstanding credentials in immunology, virology, and vaccines. He also offered incisive critiques of the ASIA theory and Dr. Sundel's ASIA-like theory of autoimmunity as related to the function of the immune system.

B. *Althen* Prong One

Petitioner has failed to prove by a preponderance of the evidence her theory causally connecting A.F.'s DTaP and IP vaccinations to her sJIA. Dr. Sundel constructed this theory based on the medical community's current understanding that sJIA is an autoinflammatory disease, the general principles of the innate immune system, and the accepted premise that the DTaP and IP vaccines are designed to elicit an immune response. Dr. Sundel concluded that even though "[d]ata looking at the potential role of adjuvants on development of complications after vaccinations are still sparse[,]" aluminum adjuvants are a contributing factor of arthritis in young girls after vaccination, "typically a booster dose." Pet'r's Ex. 23 at 5.

Petitioner's medical theory can best be described by Dr. Sundel's assertion, "was it the IP[vaccine], was it the DTaP, was it alum? I don't really know, but I do know the combination was not good for her." Tr. 88:5–9. Despite his critique that ASIA is overbroad and in need of additional study, his stated theory is based on the role of adjuvants in the development of adverse events. It is ASIA and it fails now for the same reasons it has previously failed: the diagnostic criteria proposed by the ASIA study's authors are both vague and flawed. *See, e.g.*, Resp't's Ex. G at 4; Resp't's Ex. I at 8, 13–14.

The validity of the ASIA theory has been repeatedly called into doubt in the program. *See D'Angiolini v. Sec'y of Health & Human Servs.*, 122 Fed. Cl. 86, 102 (2015) (upholding special master's "determin[ation] that ASIA does not provide[] a biologically plausible theory for recovery"), *aff'd*, 645 Fed. Appx. 1002 (Fed. Cir. 2016); *Garner v. Sec'y of Health & Human Servs.*, No. 15–063V, 2017 WL 1713184, at *8 (Fed. Cl. Spec. Mstr. Mar. 24, 2017) (observing that the ASIA theory "is, at a minimum, incomplete and preliminary—and therefore unreliable from an evidentiary standpoint"); *Johnson v. Sec'y of Health & Human Servs.*, No. 10–578V, 2016 WL 4917548, at *7–9 (Fed. Cl. Spec. Mstr. Aug. 18, 2016) (rejecting Dr. Shoenfeld's expansive medical theory that "any adjuvant [is] capable of causing any autoimmune disease," finding it "overbroad, generalized, and vague, to the point that it could apply to virtually everyone in the world who received a vaccine containing an adjuvant and then at some time in their lives developed an autoimmune disease"); *Rowan v. Sec'y of Health & Human Servs.*, No. 10–272V, 2014 WL 7465661, at *12 (Fed. Cl. Spec. Mstr. Dec. 8, 2014) (rejecting the ASIA theory because it "is not a proven theory" and no "persuasive or reliable evidence" supports it).

The primary reason for ASIA's rejection is its "changing and imprecise" diagnostic criteria, which are unable to "distinguish between afflicted and un-afflicted patients." *D'Angiolini*, 122 Fed. Cl. at 102. The "major" criteria include "dry mouth," "arthralgia" (simple joint pain), and "myalgia" (simple muscle pain); the "minor" criteria include "[o]ther clinical manifestations" and "autoimmune disease." *Id.*; *see also* Resp't's Ex. G at 4; Resp't's Ex. I at 8, 13–14. More importantly, only "two major or one major and two minor criteria" are necessary for diagnosis. *D'Angiolini*, 2014 WL 1678145, at *58. This does very little to "separate people with the disease from people without the disease." *Id.* at *59. In fact, Dr. Yehuda Shoenfeld, one of the ASIA study authors, has conceded that "every attempt for an epidemiological study has so far failed to deliver a connection" between autoimmune diseases and vaccines.[72] Resp't's Ex. J at 4.

These flaws remained unaddressed by Dr. Sundel and Dr. Gurish. Their expert reports do not add precision to the ASIA criteria, elaborate on the role of aluminum or specify how much is needed, provide any further support from scientific or medical experts in the field, or add any additional evidence to support the theory. They simply repeat what has already been rejected in the cases cited above. In fact, Petitioner's experts implicitly acknowledged the lack of success ASIA has had in the program by trying to distance themselves from the name during their testimony without distinguishing their medical theory from ASIA's premise.

And, despite distancing himself from ASIA during testimony, Dr. Sundel relied on medical literature that discussed autoimmune/autoinflammatory syndromes induced by adjuvants to support his hypothesis. He relied upon the study by Cerpa-Cruz et al.[73] to show a causal link between vaccines and autoimmune diseases. Petitioner is correct that the authors of the report conclude that their "results suggest that vaccines containing adjuvants may be associated with an increased risk of autoimmune/inflammatory adverse events following immunization." Pet'r's Ex. 23, Tab L at 4. However, this study suffers from serious limitations. As Dr. Whitton explained in his reports, the study included no control group, its population size was small, and there was an inherent selection bias. Resp't's Ex. J at 6. Additionally, as conceded by Dr. Gurish in his testimony, the study's authors themselves stated that the study's retrospective design and lack of control group make it impossible to "prove causal correlation between vaccine and clinical manifestation." Pet'r's Ex. 23, Tab L at 5. This lessens the credibility of the authors' contention that there is a correlation between sJIA alone and the various vaccines analyzed. Therefore, the study does not provide persuasive support, under the preponderant standard, for the contention that aluminum-adjuvanted vaccines can cause sJIA.

Dr. Gurish discussed the studies by Luján et al.[74] and He et al.[75] to show that aluminum adjuvant can be a contributing factor in autoimmune and autoinflammatory diseases via the

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[72] It is worth noting that ASIA is a study without an International Classification of Diseases, Ninth Revision ("ICD–9") code, which "is designed to promote international comparability in the collection, processing, classification, and presentation of mortality statistics." NAT'L CTR. FOR HEALTH STAT., https://www.cdc.gov/nchs/icd/icd9.htm (last visited May 30, 2019); *see also* Resp't's Ex. K at 2. Moreover, the study's criteria have not been substantiated by any reliable medical or scientific evidence. *See* Resp't's Ex. G at 4.

[73] *See* Cerpa-Cruz et al., *supra* note 33.

[74] *See* Luján et al., *supra* note 41.

[75] *See* He et al., *supra* note 42.

activation of macrophages. Pet'r's Ex. 29 at 5. He noted that the onset of A.F.'s sJIA four days after vaccination matches the findings of the Luján et al. study. *Id.* at 7–8. He explained that, like in those findings, the aluminum adjuvant contained in the DTaP vaccine was dispersed in A.F.'s body by entering her blood stream via macrophages, which resulted in a systemic immune response. *Id.* However, this study is not persuasive evidence for two reasons. First, as Dr. Whitton explained, it involved the administration of high doses of aluminum in sheep over a prolonged period of time. Resp't's Ex. K at 5, 8. Indeed, the study's authors noted that "[t]he content of aluminum hydroxide-based adjuvant in each dose of vaccine is of paramount importance[.]" Pet'r's Ex. 24, Tab I at 7. They explained that a vaccine with a low content of adjuvant "cannot induce immune response effectively[,]" whereas, one with a "[h]igh aluminum hydroxide content can suppress immune reactions because it can suppress the release of the antigen." *Id.* It is disingenuous to compare a single adjuvanted vaccine to aluminum hydroxide content so high that the study's authors were concerned about possible cytotoxicity.[76] *Id.* The study's findings could be better explained by aluminum toxicity rather than an acute response to a small amount of aluminum adjuvant. Second, as noted by Dr. Whitton, the sheep were given a combination of fourteen different vaccines. It is therefore impossible to determine whether a specific vaccine, if any, was responsible for adjuvant-related complications. *Id.* at 5–7. Dr. Whitton's critiques effectively render the study and its findings inapposite because it cannot link sJIA with a specific vaccine and/or adjuvant.

Dr. Gurish also relied upon the study by Bagavant et al.[77] to show that aluminum enhances autoimmune response in individuals with a specific genetic disposition to Sjögren's syndrome—an autoimmune disease. Tr. 109:21–110:10. This study, too, fails to persuade. As noted by Dr. Whitton, "when corrected for body weight, the[study] mice appear to have been given around . . . [nine hundred and twenty-four thousand] times the dose that is given in a human vaccine." Resp't's Ex. K at 8. Given the high dose administered and the absence of autoimmunity in the mice, this study's findings could also be explained by aluminum toxicity rather than the vaccination. Importantly, again, the study's authors admitted the study's limitations. Pet'r's Ex. 29, Tab K at 6. They acknowledged that the mice were dosed using routes of administration other than the intramuscular route used when administering vaccines to humans. *Id.* And, as conceded by Dr. Gurish, bio-distribution differs based on the administration route used, which "is critical to determining the ultimate reaction." Pet'r's Ex. 29 at 8. Because this study administered much higher doses of aluminum using vaccination routes other than those routinely used in humans, it fails to provide support that aluminum-adjuvanted vaccines can cause sJIA.

Petitioner has presented a theory that she is unable to distinguish from ASIA. She has correctly identified ASIA's previously identified shortcomings but failed to present any new evidence to overcome these persuasive critiques. In sum, Petitioner has failed to provide a reputable medical theory and therefore has failed to satisfy her burden under *Althen* prong one.

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[76] Cytotoxicity is "the degree to which an agent possesses a specific destructive action on certain cells or the possession of such action." *Dorland's* at 467.

[77] *See* Bagavant et al., *supra* note 39.

C. *Althen* Prong Two

Neither party disputes that A.F. developed sJIA after she received the DTaP and IP vaccines. However, that chronology of events alone is not sufficient under the preponderant standard. Both Dr. Sundel and Dr. Rose agree that the triggers of sJIA are unknown.

Dr. Sundel based his conclusion that A.F.'s sJIA was vaccine induced on the short time period between vaccination and onset of A.F.'s sJIA and on "the absence of alternative explanations" for her sJIA. *See* Pet'r's Ex. 20 at 2. Nevertheless, Dr. Sundel stated that his causation theory "is a theory only, because nobody knows what the cause of systemic JIA is." Tr. 53:1–2. He also conceded that the Chen et al.[78] study he submitted in support of his theory shows that "a direct association with even the most commonly implicated vaccines . . . has been elusive[]" because of the wide range of potential triggers. Pet'r's Ex. 23 at 3–4. Petitioner's theory does not explain the roles any of the non-adjuvanted vaccines played in the development of A.F.'s sJIA. In fact, Dr. Sundel is unable to say which, if any, of those vaccines were needed for A.F.'s symptoms to manifest. He does not apply his theory to the specific vaccinations that A.F. received.

Dr. Gurish expanded on Dr. Sundel's theory, explaining that the innate immune response is activated within hours to days of exposure to aluminum adjuvant. Pet'r's Ex. 29 at 5. He applied this timing sequence to A.F. and noted that she developed a maculopapular rash two to four days after vaccination, which was followed by abdominal pain, a swollen knee, and a recurring fever of up to 103 °F. These initial symptoms, he argued, match both the ASIA criteria and data from several studies, in particular, those by Luján et al.[79] and Bagavant et al.[80] *Id.*

Nevertheless, as discussed in *Althen* prong one above, ASIA's diagnostic criteria are unclear. First, the "exposure to external stimuli" major criterion is overbroad. Any exposure A.F. had, be it the previous otitis media, her consequent amoxicillin treatment, a viral infection, her vaccinations, or even another unidentified environmental trigger, could have activated her innate immune system's response. Second, the "appearance of 'typical' clinical manifestations" major criterion is overbroad because the symptoms listed are common and non-specific. A.F. or any otherwise healthy person with "typical" symptoms of sJIA, like fever and swollen joints, could potentially be diagnosed with sJIA.

Third, as Dr. Whitton explained, the "removal of inciting agent induces improvement" major criterion is in conflict with the [ASIA] study authors' claim that "acute infections . . . trigger long-term autoimmune disease." Resp't's Ex. I at 13. This is because infections that result in autoimmune diseases are "acute in nature" and the inciting agent in question is quickly removed once the immune system has mounted its response. In this case, A.F.'s condition would have therefore improved shortly after her immunization once the aluminum was eliminated from her system. A.F., however, continued to suffer from a rash, fever, and joint pain, as well as loss of appetite and swollen wrists and hands, for weeks after receiving the vaccines. Lastly, the "other clinical manifestations" minor criterion is a catch-all standard. Any clinical

[78] *See* Chen et al., *supra* note 28.
[79] *See* Luján et al., *supra* note 41.
[80] *See* Bagavant et al., *supra* note 39.

manifestation, e.g., myalgia, fever, arthralgia or arthritis, weakness, fatigue, sleep disturbances, and gastrointestinal, respiratory and skin disorders, can essentially be explained by ASIA. Therefore, all of A.F.'s symptomology could potentially be explained by ASIA and linked causally to the adjuvant contained in any vaccine, including those in question. Petitioner has failed to provide preponderant evidence establishing that ASIA (or the ASIA-like theory proposed by Dr. Sundel) can be applied to any specific case generally, or A.F.'s specifically.

Dr. Sundel also testified that A.F.'s sJIA was the result of a confluence of events. He likened A.F.'s condition to a "bubbling pot" created by a combination of her genetic predisposition and a variety of environmental factors, with the vaccines being "a brick [thrown] into [the pot] and it overflowed." Tr. 53:9–25. It appears Dr. Sundel may be making a *Shyface* argument, namely, that the vaccines in question were "'a substantial factor in bringing about the injury,'" but this also fails. *Shyface*, 165 F.3d at 1352. In *Shyface*, the Court affirmed the special master's findings that petitioners' minor child would not have died but for the DPT vaccination, and that the DPT vaccine contributed to his death by causing him to experience an exceptionally high fever. 165 F.3d at 1353. The Court also agreed with the special master that the concurrent sepsis was not the predominant cause of the child's death. *Id.* Although petitioners did not prove that the DPT vaccine was the only or predominant cause of their child's death, the statutory requirements were "met upon proof of the substantial factor criterion." *Id.* Unlike *Shyface*, Petitioner in the instant case has not shown that A.F. would not have developed sJIA but for the vaccines she received. A.F. was genetically predisposed to developing both MAS and sJIA. *See, e.g.*, Resp't's Ex. G at 2; Tr. 34:21–35:4, 38:25–39:6, 39:19–40:8. It was therefore highly likely that A.F. would develop sJIA at some point in her life.

Additionally, Respondent's experts argued persuasively that the facts of this case are more consistent with an alternative cause. Specifically, Respondent's experts proposed that, rather than the aluminum-adjuvanted vaccines, a viral infection was the most likely contributing factor for A.F.'s sJIA. *See, e.g.*, Resp't's Ex. A at 7–8; Resp't's Ex. J at 11–12. Dr. Whitton explained that because the effects of the small amount of aluminum contained in the vaccines in question are localized and short lived, A.F.'s sJIA could not have been caused by her vaccines. Resp't's Ex. K at 12. Rather, A.F.'s genetic predisposition and MAS, which are both commonly triggered by viral infections, support the need for "an ongoing driver" that gives rise to sJIA. *Id.*; Tr. 213:7–15; *see also* Resp't's Ex. A at 17. Dr. Rose also explained that because of A.F.'s genetic predisposition to sJIA—which is linked to the innate immune system via the cytolysis pathway—a similar MAS-like or JIA-like response would have occurred after every vaccination with an aluminum adjuvant. Resp't's Ex. A at 16–17. Because this did not occur, it is more likely that a viral infection triggered A.F.'s sJIA. *Id.* Dr. Gurish also agreed that "an ongoing driver is necessary . . . ." Pet'r's Ex. 29 at 7. As explained by Dr. Whitton, the innate immune system's response is rapid and short lived. Resp't's Ex. I at 16. It is therefore logical to assume that a constant inflammation stimulus would be required in sJIA and thus, in A.F.'s case. Finally, Dr. Rose stated that because laboratory results were negative for MAS on March 27, 2019, the only other likely explanation for A.F.'s purpuric rash is a viral infection. *Id.* at 6. Given A.F.'s genetic predisposition and the symptoms she exhibited at that time, it is more likely that this viral infection was the substantial factor that triggered her sJIA than the vaccines in question.

It should be noted that in her post-hearing reply, Petitioner stated that Respondent's experts have not offered any medical literature to support their contention that a constant stimulus of inflammation is required. Pet'r's Post-Hrg Reply at 6, ECF No. 119. She therefore argued that "such conjecture should not be accepted without the indicia of reliability that literature provides." *Id.* It appears that Petitioner is arguing that Respondent should be held to a higher standard than that for petitioners. Nevertheless, the standards "that apply to the government's proof of alternative actual causation" are the same as those that apply to Petitioner's proof of actual causation. *Knudsen*, 35 F.3d at 549. The undersigned did not hold Petitioner's assertions to a higher standard, and she will not do so for Respondent.

In sum, Petitioner has failed to demonstrate "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. She did not provide evidence that the vaccines A.F. received caused or were a substantial factor in causing her sJIA. By contrast, Respondent's experts demonstrated that a viral infection was the more likely cause for A.F.'s sJIA. For those reasons, Petitioner has failed at *Althen* prong two.

D. *Althen* Prong Three

A.F. received the DTaP and IP vaccines on March 13, 2009. Both experts agree that onset occurred sometime before April 16, 2009. They disagree on whether A.F.'s sJIA developed in mid- to late March or in early April 2009.

Petitioner bases her theory on circular reasoning and concludes that because A.F.'s injury is vaccine induced, the onset of A.F.'s symptoms establishes the appropriate time frame for a vaccine-related injury. Dr. Sundel's proposed time frame for disease onset was four to five days post vaccination. Tr. 19:13–17. He based this time frame on the contemporaneous medical records and Dr. Kimura's ultimate diagnosis of sJIA. *Id.* Dr. Rose stated that he had "no doubts that at the beginning of April [2009] A.F. had s[]JIA," but he opined that the purpuric rash she had on March 27, 2019, was not the result of sJIA, nor did she "have diagnosable MAS" at that time. Resp't's Ex. A at 6. He explained that, based on laboratory results, the more likely cause of the rash on March 27, 2019, was a viral infection, which would place the onset for sJIA in early April 2009. *Id.* at 6–7. As explained in the analysis for *Althen* prong two, based on the preponderant standard, A.F.'s sJIA was more likely caused by a viral infection. The time frame proposed by Dr. Rose is therefore more appropriate.

Additionally, none of the medical literature offered by either party discusses a medically appropriate time frame for vaccine-caused sJIA. The broader deficiencies with Petitioner's theory (which did not otherwise establish that the DTaP and IP vaccines could cause sJIA), however, render the undersigned unable to find that the timing at issue in this case of the alleged vaccine-induced sJIA has been shown to be medically acceptable. Therefore, the undersigned finds that Petitioner has not met her burden under *Althen* prong three.

VI. Conclusion

A decision on entitlement to compensation in the Vaccine Program cannot be made based on the nature and severity of the disease alone. It must reflect a thorough analysis of the

evidence and a thoughtful balance against the applicable legal standards based upon probative weight and persuasiveness. Petitioner has not established that A.F.'s DTaP and IP vaccines more likely than not caused her to develop sJIA.

Accordingly, the undersigned DENIES Petitioner's claim and DISMISSES this petition. In the absence of a timely filed motion for review filed pursuant to Vaccine Rule 23, **the Clerk of Court is directed to ENTER JUDGMENT** consistent with this decision.[81]

IT IS SO ORDERED.

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master

[81] Entry of judgment can be expedited by each party's filing of a notice renouncing the right to seek review. Vaccine Rule 11(a).